A TEXT-BOOK OF
ORGANIC CHEMISTRY

BY THE LATE

DR JULIUS SCHMIDT

ENGLISH EDITION

BY

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PREFACE

IN 1926 the late Dr H. Gordon Rule completed his translation of the well-known German text-book, Schmidt's *Lehrbuch der Organischen Chemie*. It was to a considerable extent a translation with some alterations and additions. Since that date remarkable advances have been made in organic chemistry, and the most important of these were later incorporated into the second and third editions. The size of the book remained much the same, as the space devoted to certain specialised topics was curtailed, room thus being found for subjects of more general interest, such as the electronic theory of valency, the mechanism of racemisation, isomerism due to restricted rotation round a single bond, asymmetric decomposition, factors governing the magnitude of optical rotatory power, and the parachor. Many sections of the first edition were rewritten, and altogether the value of the book was greatly enhanced, as Dr Rule, acting on various suggestions put forward by reviewers and readers, made considerable changes in the preliminary general section. The book therefore gave a comprehensive survey of the main classes of organic compounds, their properties and reactions, together with the necessary theoretical background. The success of these earlier editions showed there was a great demand for a book of this type.

Since 1936, the date of the last edition, an enormous amount of work has been done in certain fields of organic chemistry, and in preparing the present edition Dr Rule was faced with the difficult problem of including the outstanding results of these investigations without adding unduly to the size of the book. By judicious alterations and curtailments he succeeded in finding space for topics such as the electronic theory of benzene substitution, Robinson's theory of phytosynthesis of the alkaloids, and resonance, while at the same time expanding and bringing up to date those chapters dealing with the steroids, vitamins, hormones, rubber, plastics, and chemicals of therapeutic value. Dr Rule took also the opportunity to revise many sections of the book and to insert a number of corrections and, where space did not permit detailed treatment, gave suitable references to draw attention to new developments.

The complete revised manuscript was in the printer's hands when Dr Rule was incapacitated by the illness to which he succumbed.

At his request I undertook the proof-reading and indexing, with the assistance of Mrs Rule and my wife. Dr E. G. V. Percival kindly revised the carbohydrate section. Dr Rule, in his usual thorough and methodical way, had left his notes so that there could be no ambiguity about his intentions, and the book as it stands, apart from a few minor alterations, adheres strictly to his final manuscript.

NEIL CAMPBELL

EDINBURGH
May 1943

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LIST OF ABBREVIATIONS

ABBREVIATIONS	JOURNALS
Am. C. J.	American Chemical Journal.
Ann.	Liebig's Annalen der Chemie.
Ann. Chim. Phys.	Annales de Chimie et de Physique.
Ann. Rep. Chem. Soc.	Annual Reports of the Chemical Society.
Arch. Pharm.	Archiv. der Pharmazie.
Ber.	Berichte der deutschen chemischen Gesellschaft.
Biochem. J.	Biochemical Journal.
Biochem. Zeitsch.	Biochemische Zeitschrift.
Biochem. Z.	Biochemische Zeitung.
Bull. Soc.	Bulletin de la Société Chimique à Paris.
C.	Chemisches Zentralblatt.
Chem. and Ind.	Chemistry and Industry.
Chem. Rev.	Chemical Reviews.
Ch. Zeit.	Chemiker-Zeitung.
C. r.	Comptes rendus de l'Académie des Sciences.
Gazz.	Gazzetta Chimica Italiana.
Helv. Chim. Acta	Helvetica Chimica Acta.
Ind. Eng. Chem.	Journal of Industrial and Engineering Chemistry.
Ind. Eng. Chem. (Anal.)	Journal of Industrial and Engineering Chemistry. Analytical Edition.
J.A.C.S.	Journal of the American Chemical Society.
J. Biol. Chem.	Journal of Biological Chemistry.
J.C.S.	Journal of the Chemical Society.
J.C.S., A.	Abstracts of the Chemical Society.
J. Physiol.	Journal of Physiology.
J. Phys. Chem.	Journal of Physical Chemistry.
J. pr. Ch.	Journal für praktische Chemie.
J.S.C.I.	Journal of the Society of Chemical Industry.
Monats.	Monatshefte für Chemie.
Pogg. Ann.	Poggendorf's Annalen der Physik.
Proc. Chem. Soc.	Proceedings of the Chemical Society.
Proc. Roy. Soc.	Proceedings of the Royal Society.
Rec. trav. chim.	Recueil des travaux chimiques des Pays-bas.
Trans. Farad. Soc.	Transactions of the Faraday Society.
Z. anal. Ch.	Zeitschrift für analytische Chemie.
Z. ang. Ch.	Zeitschrift für angewandte Chemie.
Z. Ch.	Zeitschrift für Chemie.
Z. Elek.	Zeitschrift für Elektrochemie.
Z. Krist.	Zeitschrift für Kristallographie.
Z. phys. Ch.	Zeitschrift für physikalische Chemie.
Z. physiol. Ch.	Zeitschrift für physiologische Chemie.

ORGANIC CHEMISTRY

Introduction

COMPARATIVELY early in the history of chemistry an interest began to be taken in the remarkable variety of carbon compounds which could be prepared from plant and animal sources. This led eventually to systematic investigations on their origin and the manner in which they could be transformed one into another. It was not until the eighteenth century, however, that the first results of importance were obtained at the hands of Lavoisier. The work was found to present peculiar difficulties and to require a special laboratory technique, hence at the beginning of the nineteenth century it was severed completely from inorganic chemistry and considered as a separate branch of chemical science.[1] The name of *Organic Chemistry* originated in the belief that compounds of this type could not be prepared artificially in the laboratory, but were formed solely in living organisms under the influence of a mysterious agency termed Vital Force. Experimental evidence at first lent support to this theory, in so far that all attempts to build up such substances from materials not themselves obtained from living organisms were unsuccessful.

Faith in the Vital Force theory was shaken in 1828 by the discovery of Wöhler [2] that urea, one of the most characteristic products of animal metabolism, could be prepared from the inorganic constituents cyanic acid and ammonia.

Other syntheses followed, until it was proved beyond all doubt that the same chemical forces operated in the organic as in the inorganic world, and the assumption of a vital force responsible for the production of carbon compounds in the organism was therefore superfluous. Nevertheless there are many substances of plant and animal origin, including the very widespread class of proteins, which have so far eluded artificial preparation. Various reasons may be put forward to explain this lack of success. Not only has the precise chemical composition of the proteins yet to be determined, but even the mode of union of the atoms in these compounds is still uncertain. Nor have we any clear conception of the physico-chemical conditions under which these substances are produced in the living organism.

[1] An effort had already been made in the second half of the seventeenth century to separate organic from inorganic chemistry, by classifying each substance according to its origin as mineral, animal, or vegetable (Kopp, *Geschichte der Chemie*, 4, 241). [2] Wöhler, "Ueber kunstliche Bildung des Harnstoffs," *Pogg. Ann.*, 1828, 12.

Although we still speak of organic and inorganic chemistry, the terms are retained solely for convenience of reference. The peculiarities of organic compounds depend only on the nature of their principal constituent carbon, and the wide extent of organic chemistry is a direct consequence of the unique combining capacity of the carbon atom. No other element approaches carbon in its ability to unite with itself, atom by atom, to form open and closed chains, and as a result, the number of known carbon compounds, now well over 500,000, exceeds that of the compounds of all the other elements put together.

Organic Chemistry is thus to be defined as the chemistry of carbon compounds.[1]

As the majority of organic compounds resulting from plant and animal activity consists only of carbon, hydrogen, oxygen and less frequently nitrogen, these elements have been termed organogenetic. Organic substances containing sulphur, phosphorus and more rarely other elements are also known to occur in nature, but their number is relatively small. On the other hand, by artificial means it is possible to prepare organic derivatives of any of the elements except the rare gases.

Analytical Methods

Relatively few organic compounds are distinguished by reactions sufficiently characteristic to serve as a basis for their qualitative identification. For the separation of organic substances from mixtures there is therefore no general procedure known comparable to the systematic analysis of inorganic chemistry.

In many cases the physical properties of a substance such as smell, crystalline form, melting-point, boiling-point, or optical rotation enable it to be identified. More often it is necessary to determine its composition, first qualitatively and then quantitatively. Since no convenient method has been developed for the estimation of oxygen, this element is always determined indirectly, after the quantitative estimation of the other elements present.

QUALITATIVE ANALYSIS OF ORGANIC COMPOUNDS

Carbon and Hydrogen.—Carbon may be detected in many cases by heating the dry substance on platinum foil or in a porcelain crucible. The majority of compounds (*e.g.* starch, sugar) blacken under these conditions with the separation of carbon. Compounds which volatilise without decomposition are tested by oxidising the carbon to CO_2; the dried substance is mixed with several times its volume of copper oxide,

[1] Carbon itself and a few of its simple compounds, such as carbon dioxide and carbonates which are of frequent occurrence in the mineral world, are usually described in text-books on inorganic chemistry and are not included here.

which has previously been strongly ignited, and the mixture heated in a small dry glass tube. The formation of CO_2 can be confirmed by leading the products of combustion into lime- or baryta-water. At the same time the deposition of moisture on the colder parts of the tube indicates the presence of hydrogen in the substance under investigation.

Oxygen.—Up to the present no general method has been devised for the detection of oxygen in organic compounds.

Nitrogen.—(*a*) In many cases the presence of nitrogen may be recognised by the production on heating of the unpleasant smell of singed hair or feathers.

(*b*) In a limited number of nitrogenous substances the nitrogen can be detected by heating with soda-lime, when ammonia is evolved and may be recognised by its smell and other characteristic reactions. Nitro-compounds, amongst others, fail to give this test.

(*c*) The most reliable and sensitive method is that of Lassaigne, which consists in heating the organic substance with potassium or sodium, and converting the cyanide so formed into Prussian blue. The substance is strongly heated in a test-tube with metallic sodium (or better still potassium), and the hot tube broken by dipping into a little water. After filtration, the aqueous extract is heated for a short time with sodium hydroxide and ferrous sulphate solutions, acidified with hydrochloric acid, and treated with a few drops of a solution of ferric chloride. An insoluble precipitate of Prussian blue or a bluish-green coloration shows the presence of nitrogen in the substance tested.

Sulphur.—(*a*) On heating sodium with sulphur compounds, sodium sulphide is formed. The latter is confirmed by dissolving the product of reaction in water and testing with sodium nitroprusside (purple coloration), with a silver coin (dark brown stain), or with lead acetate solution (dark precipitate).

(*b*) Sulphur may frequently be recognised by boiling the substance (*e.g.* albumin) with a solution of lead hydroxide in alkali, when black lead sulphide is formed.

(*c*) Easily volatile substances are best heated in a closed tube with fuming nitric acid at about 200 to 300° C. (see below). Sulphur is thus oxidised to sulphuric acid, which may be tested for by dilution with water and the addition of barium chloride.

In the same way **phosphorus** may be recognised by oxidation to phosphoric acid and subsequent addition of ammonium molybdate or magnesia mixture.

Halogens.—Only in rare cases (*e.g.* hydrochlorides of bases, acid chlorides and similar easily decomposable compounds) can the halogens be tested for by direct precipitation with silver nitrate. The reason for this is that most organic halogen compounds are non-electrolytes, *i.e.*, their solutions, unlike those of inorganic halides, contain no free halogen ions. Thus chloroform may be boiled with silver nitrate without the formation of any precipitate of silver chloride.

The presence of halogens may often be proved by mixing some of the substance with freshly ignited copper oxide, and by means of a loop of platinum wire introducing a little of the mixture into a bunsen flame. In the presence of chlorine the flame is coloured first blue and then green. Bromine and iodine compounds produce a green coloration.

All organic substances containing halogen yield insoluble silver halide when they are oxidised by heating in a sealed tube with nitric acid and silver nitrate, or when the organic substance is decomposed by ignition with halogen-free calcium oxide and the product subsequently dissolved in water, acidified and treated with silver nitrate.

Detection of Metals.—It is not always possible to test for metals directly by means of the usual reagents. It is best therefore in all cases to decompose the organic substance by ignition or oxidation, and then to test for metals in the routine manner.

QUANTITATIVE ANALYSIS OF ORGANIC COMPOUNDS[1]

Estimation of Carbon and Hydrogen (Combustion). — Many celebrated names are linked with the history of this branch of organic analysis. Beginning with Lavoisier, the problem was investigated in turn by Berthollet, Saussures, Davy, and finally and most successfully by Liebig,[2] who developed a method which with small modification is still in use to-day. The details of the process are fully described in text-books of analytical chemistry and only the fundamental principles will be considered here.

A weighed amount (0·15 to 0·30 gm.) of the substance is heated with an oxygen compound (copper oxide, lead chromate) capable of readily yielding up its oxygen at a higher temperature, by which means carbon is converted into carbon dioxide and hydrogen into water. The two products of oxidation are then collected in a suitable apparatus.

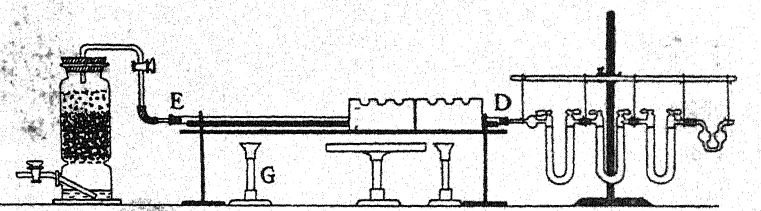


FIG. 1.

For the absorption of the water vapour produced in a combustion, a U-tube filled with calcium chloride is employed. Carbon dioxide is absorbed by means of potash in the apparatus described by Liebig, or one of its later modifications. Soda-lime is even better for this purpose.

[1] See also M. Dennstedt, *Anleitung zur vereinfachten Elementäranalyse*, Hamburg.
[2] Liebig, "Ueber einen neuen Apparat zur Analyse organischer Körper und über die Zusammensetzung einiger organischen Substanzen," *Pogg. Ann.*, 1831, **21**, 1.

The absorption tubes are carefully weighed before and after the combustion. The increase in weight of the calcium chloride tube divided by 8·9364 ($H_2 : H_2O = 2·016 : 18·016$) gives the amount of hydrogen; and the increase in weight of the potash tube multiplied by 3/11 ($C : CO_2 = 12 : 44$) gives the amount of carbon in the substance analysed.

If the compound contains nitrogen the combustion gases before leaving the tube are passed over a copper spiral heated to redness, in order to reduce any nitric oxide formed. Fused lead chromate is employed instead of copper oxide in the presence of sulphur or halogens, thus retaining as sulphate or chloride of lead the sulphur dioxide or chlorine which would otherwise be absorbed in the potash tubes. If halogens are present and sulphur absent the combustion may be carried out with copper oxide in combination with a silver spiral; the latter is kept cool and serves to remove the halogens.

In the presence of alkalis or alkaline earths, which would otherwise hold back carbon dioxide, a mixture of lead chromate and potassium bichromate is employed; the chromic acid then decomposes the carbonates formed.

Estimation of Nitrogen.—Nitrogen in an organic compound can be determined either by eliminating it in the elementary state and measuring its volume (Dumas), or by converting it into ammonia and estimating the latter gravimetrically or volumetrically (Varrentrapp-Will, Kjeldahl).

(*a*) The procedure almost universally adopted in scientific laboratories is that of Dumas. The substance is mixed with copper oxide and combusted in a tube from which all the air has been completely displaced by carbon dioxide.[1] The products of combustion are led over red-hot copper in order to reduce any oxides of nitrogen, and the free nitrogen is then collected in a graduated tube over strong potash, which removes the accompanying carbon dioxide. After completion of the combustion any nitrogen remaining in the tube is swept over into the measuring tube by a current of carbon dioxide, and the total volume of the gas read off and corrected for temperature and pressure. From the figures so obtained the percentage by weight of nitrogen in the original compound may be calculated.

Various forms of measuring tubes or "nitrometers" are available for use with the Dumas method, the type in most common use being that devised by Schiff, and illustrated in Fig. 2.

In spite of all precautions it is never possible to sweep out the last traces of air from the tube, and there remains always a residue of at least 0·2 to 0·5 c.c. The errors produced in this way are approximately balanced by the similar difficulty of removing the last traces of nitrogen from the combustion tube at the finish.

(*b*) *Kjeldahl's Method.*—This process is employed mainly in technical analysis, where a large number of similar determinations have to be

[1] The atmosphere of carbon dioxide may be generated by heating dry sodium bicarbonate or magnesite, or by means of a Kipp's apparatus.

carried out in the shortest possible time. For this purpose it excels all other methods of nitrogen estimation. The substance is heated with concentrated sulphuric acid, together with the addition of potassium permanganate, mercuric oxide or mercury. Under these conditions the organic substance is decomposed and nitrogen converted into ammonia. The latter is determined by diluting the strongly acid liquid with water, making alkaline with excess of sodium hydroxide and distilling over into a measured quantity of standard acid. After titrating back, the amount of ammonia may be calculated in the usual way. This method fails with a large number of organic substances, including pyridine and quinoline derivatives and compounds containing nitrogen linked to a second nitrogen atom,[1] although sometimes a small modification in the conditions makes successful analysis possible.[2] The process is particularly suitable for the estimation of nitrogen in plant and animal products. In academic work it will also be found of advantage in the analysis of compounds such as proteins, where, owing to the relatively low nitrogen content, a disproportionate amount of carbonaceous material has to be oxidised for each determination.

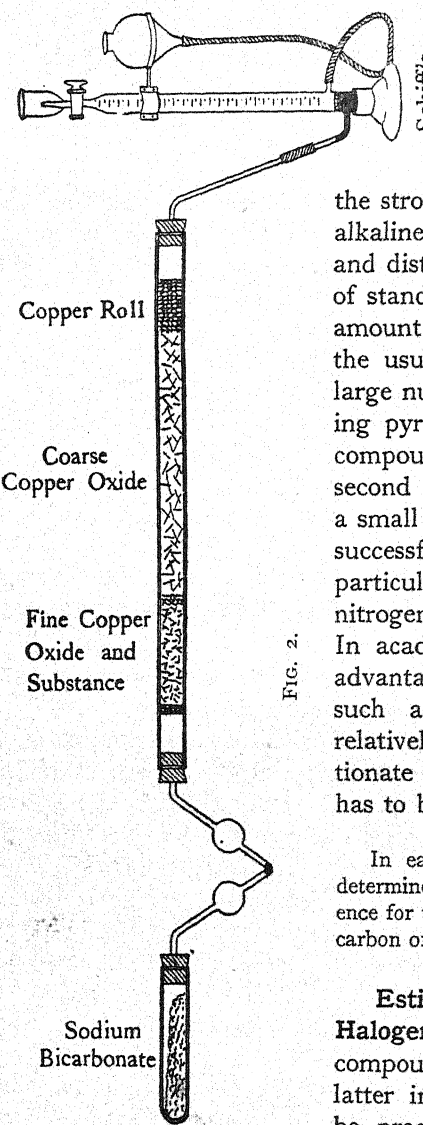


FIG. 2.

In each of the foregoing methods nitrogen is determined separately. Methods are also in existence for the simultaneous estimation of nitrogen and carbon or hydrogen, but are not yet in common use.

Estimation of Sulphur, Phosphorus and Halogens.—Vigorous oxidation of an organic compound containing *sulphur* converts the latter into sulphuric acid, which may then be precipitated by barium chloride. The oxidation may be carried out :—

(*a*) In the dry way by heating with a mixture of potassium chlorate and sodium carbonate, or potassium hydroxide and nitre, or by heating

[1] For the analysis of compounds containing nitrogen to nitrogen linkings compare Flamand and Prager, *Ber.*, 1905, **38**, 559. [2] Nitro- and cyano-compounds must first be mixed with sugar, and nitrates with benzoic acid; compare *Ber.*, 1894, **27**, 1633; Dyer, *J. C. S.*, 1895, **67**, 811, 817; *C.*, 1898, **II**, 312.

with sodium carbonate and mercuric oxide. More recently sodium peroxide has been used as the oxidising agent.[1]

(*b*) In the wet way by heating in a sealed tube with concentrated nitric acid at 150-300° (Carius).

(*c*) A reliable modern method [2] is to heat the substance in a stream of oxygen, using fine platinum gauze as catalyst. The sulphur dioxide evolved is absorbed in a solution of bromine in sodium hydroxide, by which it is oxidised to sulphuric acid.

In order to determine *phosphorus* in an organic compound the latter may be oxidised to phosphoric acid and estimated with magnesia mixture. For this purpose the methods of oxidation already described above are suitable.

In some cases it is convenient to oxidise sulphur and phosphorus in the wet way, by use of potassium permanganate and potassium hydroxide, or with bichromate and hydrochloric acid.

Similarly in the estimation of the *halogens* it is usual to oxidise the organic substance completely, before converting the halogen into silver halide. In solutions of hydrochlorides of organic bases the halogen can be directly precipitated with silver nitrate.

(*d*) From early times halogen has been estimated by decomposing the organic substance with halogen-free quicklime at a high temperature. The simplest procedure is to mix the substance with lime and to heat in a short, narrow combustion tube. When the reaction is complete the contents of the tube are dissolved in nitric acid, carbon and splinters of glass are filtered off, and the halide precipitated with silver nitrate or determined volumetrically. This method is of universal application, although inconvenient in the case of volatile substances, owing to the longer tube required and the larger quantity of lime to be brought into solution.

(*e*) A method which leapt at once into favour is that first suggested by Carius in 1860, improved in 1865, and five years later modified to the form commonly in use to-day. It resembles the estimation of sulphur (see above) in that the substance is heated with concentrated nitric acid and silver nitrate in a sealed tube at 200-300°, the halogen being obtained directly as silver halide.

Sodium peroxide has also been proposed for the determination of halogen.

(*f*) Attention has lately been drawn to a method recommended by Baubigny and Chavanne, in which the substance is heated to 130-140° with a mixture of potassium bichromate and concentrated sulphuric acid, in the presence of silver sulphate or nitrate.[3] The escaping chlorine or bromine is absorbed in a sulphite solution, and titrated as halogen acid, while iodine remains behind as hydriodic acid. In the case of chlorine and bromine estimations, D. Vorländer [4] substitutes mercuric

[1] Pringsheim, *Ber.*, 1903, **36**, 4244; **37**, 2155. [2] H. Apitzsch, *Z. ang. Ch.*, 1913, **26**, 503.
[3] H. Emde, *J. C. S.*, 1911, A, ii, 532. [4] D. Vorländer, *Ber.*, 1919, **52**, 308.

oxide or nitrate, the silver salt being necessary only in the presence of iodine. A simple and rapid method of accurately determining chlorine and bromine by oxidation with chromic acid mixture, and trapping the liberated halogen in alkaline hydrogen peroxide, has been devised by P. W. Robertson.[1] These modifications are found to be of general application and—except for the analysis of volatile substances—may eventually displace the Carius method from laboratory practice.

(*g*) A simple method of estimating halogen in organic compounds,[2] especially benzene derivatives, consists in the combustion of the substance in a Dennstedt apparatus (see below), the halogens being absorbed in alkaline sulphite and subsequently titrated.

(*h*) It is also possible to reduce the halogen in many compounds (*e.g.* the halogen substituted fatty acids) by means of nascent hydrogen. In these cases the substance is treated with water and sodium amalgam, and shaken frequently during the course of several hours. The aqueous solution is then decanted from the mercury, the latter washed with water and the combined solutions acidified with nitric acid. The halogen is estimated either volumetrically or gravimetrically. Those compounds containing halogen attached to an aromatic ring do not lose it under this treatment. On the other hand, the method of Stepanow, as modified by Bacon, for the estimation of halogen by reduction with sodium and alcohol gives satisfactory results even with aromatic derivatives.[3]

Estimation of Metals and Inorganic Acids.—In most cases the metals are determined by routine inorganic analysis, after the organic substance has been decomposed either by heating to redness, or by oxidation in the wet or dry way, according to the nature of the metals present.

Frequently the metals may be estimated simultaneously with carbon and hydrogen, by combusting the substance in a porcelain boat in a current of oxygen (*e.g.* silver salts of organic acids).

The inorganic acids present in salts of organic bases can usually be determined in the customary manner.

Estimation of Oxygen.—The oxygen content of an organic compound is always estimated by difference.

Dennstedt's Method of Analysis[4]

In the Dennstedt method, which has largely displaced that of Liebig, the combustion is carried out in oxygen in the presence of platinum as catalyst. The products of combustion, water and carbon dioxide are trapped in weighed tubes containing calcium chloride and soda-lime respectively.

Compounds containing *nitrogen* yield in addition nitrogen peroxide, which must not be permitted to pass into the absorption apparatus. The gases are therefore led over suitably heated lead dioxide, when the

[1] P. W. Robertson, *J. C. S.*, 1915, **107**, 902. [2] K. Dachlauer and C. Thomsen, *Ber.*, 1924, **57**, 559. F. Arndt, *ibid.*, p. 763. [3] Stepanow, *Ber.*, 1906, **39**, 4056. C. W. Bacon, *Chem. News*, 1909, **99**, 6. Walker and McRae, *J. Am. C. S.*, 1911, **33**, 598. [4] M. Dennstedt, *Anleitung zur vereinfachten Elementäranalyse*, Hamburg.

nitrogen peroxide is retained as lead nitrate. If the substance contains *sulphur*, this element becomes oxidised to sulphur dioxide and trioxide, both of which are absorbed by the lead peroxide to form lead sulphate. Since the latter may be extracted quantitatively, it is possible to estimate the carbon, hydrogen and sulphur simultaneously.

Similarly lead dioxide completely absorbs *chlorine* and *bromine*, which are liberated on combustion either as such or as the hydrogen compounds. *Iodine* is always eliminated in the free state and removed by means of " molecular " silver contained in a porcelain boat. If the substance under consideration is free from nitrogen and sulphur, the amount of iodine is given directly by the increase in weight of the boat. This is also the simplest way of estimating chlorine or bromine in the absence of nitrogen. In cases where nitrogen or sulphur, or both, are present in addition to halogens, the silver halide formed is mixed with nitrate or sulphate. For the simultaneous estimation of halogen, or halogen and sulphur, under these conditions, reference should be made to the original paper of Dennstedt already quoted.

Simplified methods of **microanalysis** for organic compounds have also been submitted to careful investigation in the last few years and are now universally employed.[1]

In principle these do not differ much from the routine methods, but are carried out with the use of very small quantities. Carbon and hydrogen are oxidised with copper oxide and lead chromate in a stream of oxygen. The CO_2 and H_2O are absorbed in the usual way; nitrogen is estimated volumetrically by the Dumas method. The few milligrammes of the substance employed are weighed on a micro-balance, and the whole apparatus is much reduced in size. The advantages of the method lie not only in a saving of gas and time but above all of material. The last point is of the greatest importance, more particularly since research in organic chemistry is extending more and more to biochemical processes, from which in many cases only minute quantities of valuable products can be isolated.

CALCULATION OF EMPIRICAL FORMULÆ

The formula of the substance is deduced from the percentage composition, as found by analysis, in the same way as with inorganic compounds. The percentage figures are first divided by the atomic weights of the elements to which they have reference; the quotients thus obtained show the relative proportions in which the atoms are combined together. On using the smallest of these quotients as a divisor for the others, values are arrived at which either approximate to whole numbers or do so after further simple multiplication. The formula finally deduced should be in accordance with the Law of Even Numbers.

[1] See F. Pregl, *Quantitative Organic Microanalysis*, translated by E. Fyleman (Churchill).

Example.—The analysis of a substance consisting of carbon, hydrogen, nitrogen, chlorine and oxygen gave

44·05% C, 7·38% H, 10·18% N, 26·19% Cl, and by difference 12·20% O.

The divisions	$\frac{44\cdot05}{12}$,	$\frac{7\cdot38}{1}$,	$\frac{10\cdot18}{14}$,	$\frac{26\cdot19}{35\cdot5}$,	$\frac{12\cdot20}{16}$ yield the
figures	3·59,	7·38,	0·73,	0·74,	0·76

These divided by 0·73 give

4·92,	10·01,	1·0,	1·01,	1·04

From which the simplest formula is $C_5H_{10}ONCl$.

The simplest formula obtained in this way is termed the *empirical formula*, and does not always correspond to the real molecular weight, which may prove to be some higher multiple thereof.

After discovering the percentage composition of a substance and with it the proportions in which the atoms are united together, the next problem is to ascertain the true molecular weight.

DETERMINATION OF MOLECULAR WEIGHT—MOLECULAR FORMULA OF AN ORGANIC COMPOUND

It is frequently possible to deduce the probable molecular weight of a compound from the reactions by which it is formed. In other cases the information can be gained from a detailed chemical investigation of the nature of the substance. In most instances, however, the best results are given by physical methods.

Determination of Molecular Weight by Chemical Methods

It should be said at once that an absolutely sure method of determining molecular weights by purely chemical means is not available. It is only possible to eliminate certain of the values in question and to estimate with some probability the actual size of the molecule.

For this purpose derivatives of the substance must be prepared possessing an atom or radical capable of being quantitatively determined, from the proportion of which the molecular formula of the derivative may be calculated and hence that of the parent substance.

Salt-forming compounds, such as acids and bases, lend themselves best to this end. In the case of acids the determinations are carried out preferably with the silver salts, because these are usually of normal composition and easily analysed. In addition it is necessary to know the basicity of the acid, which may be ascertained from an examination of the esters or salts. As will be seen later (p. 78) the electrical conductivity also gives valuable information on this point.

For similar reasons the determination of the molecular weight of a base is carried out by means of its platinum salt, which is generally of the type of ammonium chloroplatinate, $(NH_3)_2H_2PtCl_6$, and thus contains 1 mol. of hydrochloroplatinic acid, H_2PtCl_6, for each 2 mols. of a monacid or 1 mol. of a diacid base.

The proportion of platinum in the double salt is estimated by ignition, and from this is calculated the total weight of the other constituents associated with one atom of platinum (at. wt. 194·8). By subtracting the weights of six atoms of chlorine and two atoms of hydrogen from the number so obtained, and subsequent division by 2 (for a monacid base), the molecular weight of the base is found.

Under certain conditions the molecular weight of a base may also be determined by estimating the amount of hydrochloric acid in the hydrochloride.

Example I.—Acetic acid on analysis gives the empirical formula CH_2O. It is a monobasic acid, and in silver acetate one hydrogen atom of the acid is therefore replaced by one atom of silver. Hence in order to find the molecular weight of acetic acid we only require to estimate the amount of silver in the silver salt.

0·4120 gm. silver acetate leaves on ignition 0·2665 gm. metallic silver. The salt therefore contains 64·70 per cent. silver ; or

100 parts of silver acetate consist of—

Organic residue . . .	= 35·3
Silver	= 64·7

The molecular weight of the organic residue in silver acetate is therefore given by the equation

$$64{\cdot}7 : 35{\cdot}3 = 107{\cdot}88^{1} : x$$
$$x = 59.$$

Free acetic acid, however, contains in addition to these 59 parts of acetic acid residue a further atom of hydrogen. The molecular weight of the free acid is therefore 60. The simplest formula CH_2O arrived at through analysis, and corresponding to the mol. wt. 30, must accordingly be doubled, and the composition of acetic acid expressed by the formula $C_2H_4O_2$.

This is termed the *molecular formula* and indicates how many atoms of the elements composing the compound are contained in one molecule.

Example II.—Analysis of aniline shows it to consist of 77·42 per cent. C, 7·53 per cent. H, and 15·05 per cent. N : from which is derived the empirical formula C_6H_7N. As is well known, NH_3 combines with HCl to form ammonium chloride in the proportion of 17 : 36·4. Aniline also combines directly with hydrochloric acid to form a similar salt. The molecular weight of aniline may therefore be considered to be that amount which combines with 36·4 gms. HCl, and may be calculated from the chlorine content of aniline hydrochloride. On precipitation with silver nitrate, 0·2590 gm. of this salt gives 0·2870 gm. of silver chloride, which corresponds to 0·073 gm. of HCl. Consequently 0·259 gm. of the salt contains 0·073 gm. of HCl, and by difference 0·186 gm. of aniline. From this it follows from the equation

$$0{\cdot}073 : 0{\cdot}186 = 36{\cdot}4 : x$$

that 93 parts by weight of aniline are united with 36·4 parts of HCl.

The empirical formula C_6H_7N also gives 93 as the molecular weight and is therefore to be considered as the molecular formula of aniline.

Example III.—Caffeine, the physiologically active constituent of coffee and tea, gives on analysis the empirical formula $C_4H_5N_2O$.

It is a monacid base, and its platinum compound consists therefore of 2 mols. of caffeine combined with 2 mols. of hydrochloric acid and 1 mol. of platinum chloride.

[1] Atomic weight of silver.

On ignition 100 parts by weight of this compound give 24·6 parts of metallic platinum; consequently the weight containing one atomic proportion (194·8) of platinum is

$$\frac{194{\cdot}8 \times 100}{24{\cdot}6} = 791{\cdot}8.$$

These 791·8 parts of the platinum double salt consist however of 2 mols. of caffeine combined with $2HCl+PtCl_4$; the molecular weight of caffeine is therefore obtained from the equation

$$2x+(2\times 36{\cdot}4)+336{\cdot}3 = 791{\cdot}8$$
$$x = 191.$$

The formula $C_4H_5N_2O$ quoted above, and corresponding to the mol. wt. 97, must therefore be doubled, giving the molecular formula of caffeine as $C_8H_{10}N_4O_2$.

The majority of organic compounds are neither acids nor bases, and with indifferent substances such as these it is frequently impossible to determine the molecular weight by purely chemical methods. Sometimes a detailed study of the reactions of the substance leads to a definite conclusion.

Investigation may be made, for example, as to the manner in which the compound behaves on the substitution of hydrogen by chlorine, and the proportion of the total hydrogen which is replaceable in this way.

Example I.—Chloro-substituted carboxylic acids can be prepared by the direct action of chlorine on the acids. Acetic acid, with the empirical formula CH_2O, gives according to experimental conditions three different acids on treatment with chlorine, the final product of substitution having the formula $C_2HO_2Cl_3$. In acetic acid itself there are therefore three hydrogen atoms replaceable by chlorine, pointing to the molecular formula $C_2H_4O_2$ for acetic acid.

Example II.—The simplest formula for naphthalene as deduced from analytical data is C_5H_4. Naphthalene reacts with chlorine, however, to give a substance, monochloronaphthalene, containing 73·8 per cent. C, 4·3 per cent. H and 21·9 per cent. Cl, from which the formula $C_{10}H_7Cl$ is derived. This compound is produced from naphthalene by the substitution of hydrogen by chlorine, so that at least one whole atom must have been replaced, since fractions are excluded. From the formula $C_{10}H_7Cl$, therefore, it is obvious that at least $\frac{1}{8}$ of the total hydrogen in the original compound has been replaced, and naphthalene contains in consequence 8, or 2×8, or 3×8, etc., hydrogen atoms, together with 10 (or a multiple of 10) carbon atoms. A multiple of 8 or 10 is, however, out of the question, since no derivatives have ever been obtained from naphthalene indicating the possibility of replacing, for example, $\frac{1}{16}$ or $\frac{1}{32}$ of the total hydrogen. For these reasons the formula C_5H_4 is doubled, and the molecular formula $C_{10}H_8$ assumed for naphthalene.

In some cases an investigation of the additive compounds given with picric acid has been of service in determining the molecular weights of hydrocarbons.[1]

Example III.—An illustration of the manner in which the chemical examination of even more complicated compounds may throw light upon the molecular weight is given in the case of fructose, which has the same percentage composition as acetic acid, and therefore the empirical formula CH_2O. This compound on reduction is converted into mannitol, which may be transformed back to fructose by oxidation. The molecular

[1] See F. W. Küster, *Ber.*, 1894, **27**, 1101.

weight of mannitol is known, since it is a hexahydric alcohol $C_6H_8(OH)_6$, derived from hexane C_6H_{14}, and may be converted into this hydrocarbon. Consequently fructose similarly contains six atoms of carbon and has the molecular formula $C_6H_{12}O_6$.

Determination of Molecular Weight by Physical Methods [1]

Of the many processes available for this purpose, those which have proved of greatest service to the organic chemist are the determination of vapour density by Victor Meyer's method, and the determinations of molecular weight by measuring the elevation of boiling-point or the depression of freezing-point of a solution. These are described in full detail in analytical text-books.

Polymerism

It is seen from the foregoing pages that compounds of the same percentage composition may possess different molecular weights and therefore different properties. Such compounds are said to be **polymers** or **polymerides.** The number of organic compounds exhibiting this relationship is very large, familiar examples being cyanic acid, HCNO, and cyanuric acid, $(HCNO)_3$; formaldehyde, CH_2O, and fructose, $C_6H_{12}O_6$.

Molecular Structure and Isomerism

Even supposing the composition and molecular weight of a substance to have been determined by means of the methods indicated in the previous chapter, the molecular formula arrived at from these data is not yet sufficiently characteristic to obviate the possibility of confusion with other substances. There are numerous organic compounds of the same percentage composition and molecular weight which nevertheless differ in their physical and chemical properties. Such substances are called **isomers,**[2] or **isomerides.**

For example, five different compounds are known having the composition and molecular formula C_3H_6O, and ethylamine and dimethylamine of the same molecular formula C_2H_7N show considerable differences in their chemical and physical behaviour.

The reason for such differences must be sought in the internal structure of the molecules, which are assumed to contain a dissimilar *arrangement* of atoms. This difference of arrangement may refer :—

(*a*) To the manner in which the atoms are linked together, without reference to their positions in space. These are cases of **structural isomerism,** and are treated in detail under the theory of structure.

(*b*) To the relative position of the atoms in space. These are cases of **stereoisomerism** and are discussed under stereochemistry.

[1] Two simple micro-methods of determining molecular weights have been described by G. Barger (*J. C. S.*, 1904, **85**, 286 ; see also K. Rast, *Ber.*, 1921, **54**, 1979) and by K. Rast (*Ber.*, 1922, **55**, 1051. [2] The term *metamerides*, which was applied to such substances by Berzelius, is less frequently used nowadays and employed only in special cases of isomerism (see p. 20).

It is a point of interest that the development of these two branches, which together comprise the theory of molecular structure, originated solely in the sphere of organic chemistry.[1]

I.—STRUCTURE

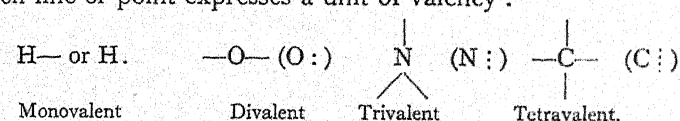
The theory of the structure of organic compounds deals with the manner in which the atoms are connected one with another, and is based on the conception of valency.

(*a*) Outline of the Theory of Valency

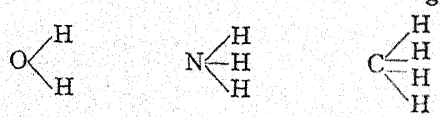
In the year 1858 Kekulé advanced two hypotheses which form the foundation of modern views on the structure of carbon compounds. They postulated that carbon is a tetravalent element and that its atoms have the power to combine one with another.[2] Somewhat later Couper [3] published similar views, which gave rise to the idea of atomic linkings.[4]

Whereas at first it was assumed that the different atoms forming a molecule were held together in such a manner that one attracted all or a certain number of the others, and these themselves exerted a reciprocal attraction on the first, thus holding it in position, it was realised later that this mutual influence extended only from atom to atom. Graphically expressed, the atoms are conceived as strung into a chain, each member being linked to those adjacent to it; if one be removed and not replaced by another, the chain breaks and the compound decomposes. Such chains may be built up from a variety of atoms which need not be of the same valency. A monovalent atom such as hydrogen, however, has only the one opportunity of union, whilst one which is divalent has two, and so on.

The power of union or valency of an atom is indicated by placing small lines or points close to the symbols of the elements, in such a way that each line or point expresses a unit of valency:



Assuming that in the formation of a compound these valencies are mutually used up, it follows that those elements which combine with hydrogen according to the formula X—H must, like hydrogen, be monovalent. The elements which combine according to the formulæ



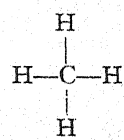
are then di-, tri- and tetravalent respectively.

[1] The phenomenon of isomerism is comparatively rare in inorganic chemistry. [2] *Ann.*, 1858, **106**, 151. [3] *Ann. chim. phys.*, 1858 (3), **53**, 469. [4] It should be noted that Kekulé and Couper are not the actual founders of the theory of valency. This honour belonged to Frankland and Kolbe. The former investigators have, however, rendered the great service of expanding the ideas of Frankland and Kolbe, and of applying them to organic chemistry.

The further development of the theory of valency in inorganic chemistry is complicated by the fact that elements do not always exhibit the same valency; thus copper is mono- or divalent according to whether it is present in a cuprous or a cupric compound. In organic chemistry the conditions are simpler, since the elements H, O, and C, of which the majority of important carbon compounds are composed, show with comparatively few exceptions a constant valency. In other words, hydrogen is monovalent, oxygen generally divalent [1] and carbon tetravalent.

The manner in which the atoms are linked up within the molecule indicates the constitution or structure of the compound, and is expressed by means of constitutional or structural formulæ. These are built up according to the following rules, based on experience :—

1. *The carbon atom is usually tetravalent*, in agreement with its position in the periodic classification. A carbon atom may thus combine with a maximum of four monovalent atoms or groups. This is illustrated by one of the simplest organic compounds, marsh gas or methane, in which one atom of carbon is combined with four atoms of hydrogen.



Methane.

In a few compounds such as carbon monoxide, C=O, fulminic acid, HO—N=C and others, carbon plays the part of a divalent element. It may also exist in the trivalent state in triphenylmethyl, and other compounds.

2. *The four valencies of carbon are equivalent to one another*, since the replacement of any one of the four hydrogen atoms in methane by the same monovalent atom, or group of atoms, always yields the same mono-substitution product.

Henry [2] sought to prove the equivalence of the four carbon valencies by preparing nitro-methane, $CH_3(NO_2)$, by four different methods, so that the nitro-group each time replaced a different hydrogen atom of methane. If these hydrogen atoms are distinguished by the indices *a*, *b*, *c*, and *d*, the compounds prepared may be written as follows,

$$C(NO_2)_aH_bH_cH_d \qquad CH_a(NO_2)_bH_cH_d \qquad CH_aH_b(NO_2)_cH_d$$

and

$$CH_aH_bH_c(NO_2)_d,$$

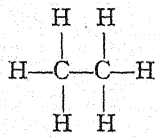
all of which proved to be identical.

This proof was subsequently invalidated by the discovery that the ingoing atom or group does not necessarily assume the position originally occupied by the atom or group which is being displaced (see Walden inversion). The equivalence of the four carbon valencies is, however, established by the fact that compounds such as CCl_4 possess zero dipole moment (see p. 82).

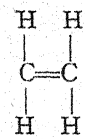
[1] It should be borne in mind that oxygen in organic compounds may under special conditions be tetravalent (see Collie and Tickle, *J. C. S.*, 1899, **75**, 710; and Baeyer and Villiger, *Ber.*, 1901, **34**, 2685) and carbon possibly trivalent. [2] *C. r.*, 1887, **104**, 1106; *Z. phys. Ch.*, 1888, **2**, 553; *C.*, 1907, **1**, 1312.

3. *Carbon atoms have a great capacity for combining with one another.* Recognition of this fact was of the greatest importance for the development of structural chemistry, since it led directly to the possibility of writing constitutional formulæ for carbon compounds. In the union of carbon atoms it is supposed that each atom is bound by a valency, or several valencies, to a neighbouring atom; the remaining valencies can then be saturated by hydrogen, or other simple or complex groups. Two carbon atoms may thus be linked together with one, two, or three valencies, these being termed single, double, or triple bonds respectively, *e.g.* C—C, C=C, C≡C.

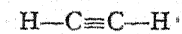
Those substances in which, as in I, only singly bound carbon atoms occur, are called saturated carbon compounds, whereas those, as in II and III, containing double or triple bonds are known as unsaturated.



I. Ethane

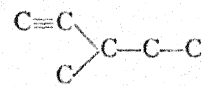


II. Ethylene

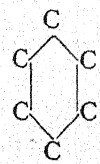


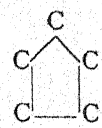
III. Acetylene.

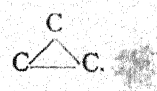
In a similar way it is possible for three, four, or any larger number of carbon atoms to combine together. The final product may be an open chain such as



or closed chains or rings of the type

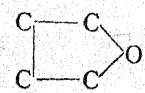


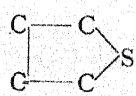


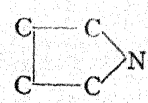


A number of important open chain carbon compounds are found in animal and vegetable fats. Consequently that section of organic chemistry which treats of open chain compounds is known as the fatty series, and a substance belonging to this class as a *fatty* or *aliphatic compound.*

On the other hand, those containing closed chains come under the heading of *cyclic compounds.* If the rings consist entirely of carbon atoms, as in the above examples, they are termed *carbocyclic*; if in addition to carbon we have elements such as oxygen, sulphur or nitrogen, taking part in the formation of rings of the type





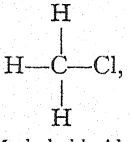


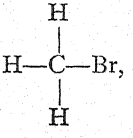
the compounds are termed *heterocyclic.*

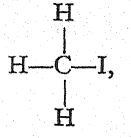
Among the carbocyclic rings, the one containing six carbon atoms with six free valencies possesses a special interest. From it are derived substances classed as *aromatic compounds* or *benzene derivatives*.

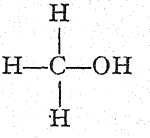
(*b*) Substitution, Radicals, Isomerism

Under suitable conditions the elements in organic compounds may be replaced, or substituted, in equivalent proportions by other elements. Once again considering the simplest compound of carbon, methane, it is possible for one of its hydrogen atoms to be replaced by one atom of chlorine, bromine or iodine, or by a group of atoms, such as .O.H, having one free bond :—


Methyl chloride


Methyl bromide


Methyl iodide


Methyl alcohol.

Such groups of atoms, which still exhibit free affinity and therefore are not stable in the free state, are often transferable as such from one compound to another, and are termed **radicals** or **groups**. The group OH is known as hydroxyl, and since it possesses only one free affinity is monovalent. By the removal of successive atoms of hydrogen from methane we may derive the following :

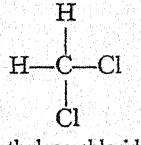
Methyl

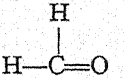
Methylene

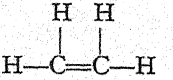
Methenyl or methine.

which are mono-, di- and trivalent radicals respectively.

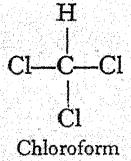
In the same way it is easy to understand that two atoms of hydrogen may be replaced either by two monovalent atoms or groups, or by one divalent atom or group, as illustrated in the following examples :

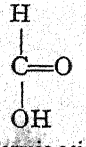

Methylene chloride

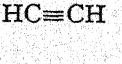

Formaldehyde


Ethylene.

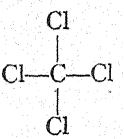
Similarly three hydrogen atoms of methane may be substituted by three monovalent atoms or radicals, by one monovalent and one divalent atom (or radical), or by a trivalent atom (or radical), as in the following compounds :


Chloroform

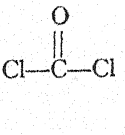

Formic acid


Acetylene.

Finally, all four hydrogen atoms may be replaced by four monovalent atoms or radicals, etc., as in—



Carbon tetrachloride



Phosgene

Carbon dioxide.

The substitution of hydrogen in methane by the radical CH_3 will be considered in more detail. When an atom of hydrogen in CH_4 is exchanged for the monovalent radical CH_3, the hydrocarbon ethane, $H_3C—CH_3$, is produced. If in this compound H is again replaced by CH_3, we obtain $CH_3—CH_2—CH_3$, propane. Obviously there is only one ethane or propane possible, since it is immaterial which hydrogen atom in methane or ethane is substituted. If, however, a hydrogen atom in propane is once again exchanged for CH_3, two isomeric compounds may be formed, according to whether the H replaced is situated in one of the two CH_3 groups or in the CH_2. In the first case normal butane is obtained

$$H_3C—CH_2—CH_2—CH_3$$

Normal butane

and in the second isobutane,

$$H_3C—\underset{\displaystyle CH_3}{\underset{|}{CH}}—CH_3$$

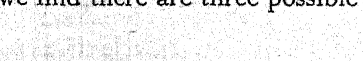
Isobutane

both of the composition C_4H_{10}.

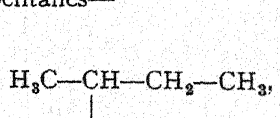
As in numerous other cases, the cause of isomerism in the butanes is the different constitution of the carbon chains. Normal butane contains a straight carbon chain, whereas isobutane has a branched chain.

Isomerism of this type involving a different structure, or manner of linking, of the carbon chain or nucleus is termed **chain** or **nuclear isomerism.**

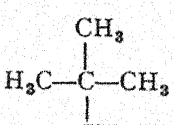
It is seen from the foregoing that there are two ways of linking up four carbon atoms ; and if in a similar manner we derive from the formulæ of the two butanes the corresponding compounds with five carbon atoms, we find there are three possible pentanes—



Normal pentane



Isopentane



Neopentane or tetramethyl methane.

With an increasing number of carbon atoms, the number of different modes of linking, and therefore the possible number of isomers, increases

with extraordinary rapidity. There are five hexanes, C_6H_{14}, nine heptanes, C_7H_{16}, and eighteen octanes, C_8H_{18}, theoretically possible.

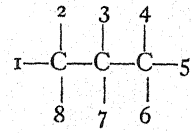
It is also possible for hydrogen atoms in all these hydrocarbons to be replaced by other elements or radicals. This gives rise to a different kind of isomerism from that discussed above. For example, different chlorine compounds may be derived from propane, $CH_3.CH_2.CH_3$, according as the halogen replaces hydrogen in the CH_2 or one of the CH_3 groups—

$H_3C—CH_2—CH_2Cl$	and	$H_3C—CHCl—CH_3$
Normal propyl chloride		Isopropyl chloride.

The reason for the difference between these two compounds is no longer to be found in the different structure of their carbon chains, but in the different position of the chlorine atom in the same carbon chain.

Isomerism caused by the different position of substituents in the same carbon chain is termed **position isomerism.**

This can lead to conditions of great complexity, particularly when the carbon framework is saturated with different monovalent atoms or groups. It is thus theoretically possible to form over one hundred different derivatives of propane, C_3H_8, if in the annexed formula the numbers 1 to 8 represent different monovalent atoms.



(*c*) Homologues, Metamerism

If we compare the formulæ of the simple hydrocarbons derived from methane by substitution, as described in the previous section,

CH_4	C_2H_6	C_3H_8	C_4H_{10}
Methane	Ethane	Propane	Butane,

we observe at once that each member of the series differs in its composition by CH_2 from the following member. Indicating the number of carbon atoms in these hydrocarbons by n, where n may be any whole number from 1 upwards, the number of hydrogen atoms is given by $2n+2$, and the series possesses the common formula C_nH_{2n+2}.

In all these hydrocarbons we may replace the hydrogen atoms by other atoms or radicals. On substituting a hydrogen atom in the above four hydrocarbons by a hydroxyl group, we obtain, irrespective of possible isomerides, the following compounds :

$CH_3.OH$	$C_2H_5.OH$	$C_3H_7.OH$	$C_4H_9.OH$
Methyl alcohol	Ethyl alcohol	Propyl alcohol	Butyl alcohol.

In this series also, each member differs from the next by CH_2, and all are expressed by the general formula $C_nH_{2n+1}.OH$.

Substitution by the most varied elements or radicals always results in the formation of groups of bodies whose members differ from one to another by CH_2.

A group of similarly constituted compounds of this type is termed a **homologous series,** and its individual members **homologues.** It is easily understood that compounds which differ merely in the replacement of H by CH_3, and are otherwise of similar structure, possess for the most part the same chemical properties. Thus the hydrocarbons CH_4, C_2H_6, C_3H_8, C_4H_{10}, show great similarity in chemical behaviour, and the same is true of the hydroxyl compounds, CH_3OH, C_2H_5OH, C_3H_7OH, C_4H_9OH. Many other such series are met with in organic chemistry, and in consequence the study of the subject is very much lightened.

It has been shown by Kopp that in a homologous series the physical properties of the compounds change gradually from member to member (p. 77).

The expression **metamerism,** which is seldom employed nowadays, refers to that kind of isomerism involving radicals attached to a polyvalent element. Numerous examples of this kind are known, of which the following will serve as illustrations :—

General Formula	Butylamine	Ethyl dimethylamine
$C_4H_{11}N$	$\left.\begin{matrix}C_4H_9\\H\\H\end{matrix}\right\}N$	$\left.\begin{matrix}C_2H_5\\CH_3\\CH_3\end{matrix}\right\}N$

	Dipropyl ether	Methyl-pentyl ether	Ethyl-butyl ether
$C_6H_{14}O$	$\left.\begin{matrix}C_3H_7\\C_3H_7\end{matrix}\right\}O$	$\left.\begin{matrix}CH_3\\C_5H_{11}\end{matrix}\right\}O$	$\left.\begin{matrix}C_2H_5\\C_4H_9\end{matrix}\right\}O$
	Butyric acid	Methyl-propionate	Ethyl acetate
$C_4H_8O_2$	$\left.\begin{matrix}C_4H_7O\\H\end{matrix}\right\}O$	$\left.\begin{matrix}CH_3\\C_3H_5O\end{matrix}\right\}O$	$\left.\begin{matrix}C_2H_5\\C_2H_3O\end{matrix}\right\}O$

(*d*) Constitution of Unsaturated Carbon Compounds

Many instances of unsaturated compounds are known in organic chemistry, and these have for long been a fruitful subject of investigation. Earlier work in this direction led to the assumption of double and triple bonds, as illustrated in the formulæ—

$H_2C{=}CH_2$ Ethylene $\qquad$ $HC{\equiv}CH$ Acetylene.

A number of unsaturated carbon compounds is also known in which the presence of a divalent carbon atom is assumed,[1] as in

C : O Carbon monoxide $\qquad$ C : S Carbon monosulphide $\qquad$ C : NH Hydrogen cyanide $\qquad$ C : NOH Fulminic acid.

Nevertheless it should be noted that this hypothesis of multiple bonds is not indispensable for the explanation of unsaturated compounds, although it is still accepted by the great majority of chemists despite the objections that have been brought against it.

[1] See, however, p. 88, l. 11.

The theory of the existence of double and multiple bonds arose from the observation that all those reactions which would be expected to yield methylene, CH_2, invariably lead to the formation of its homologue, ethylene, C_2H_4. It was therefore assumed that free valencies could not exist on the carbon atom, and consequently of the two formulæ proposed for ethylene, $H_2C{=}CH_2$ and $H_3C{-}CH{=}$, Erlenmeyer decided in favour of the first.

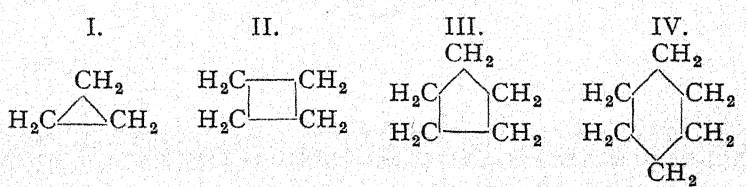
The most characteristic property of unsaturated compounds is their ability to add on elements or radicals and pass into saturated compounds, for example—

$$\underset{\text{Ethylene}}{H_2C:CH_2} + H_2 = \underset{\text{Ethane.}}{H_3C.CH_3}$$

Doubly bound carbon atoms appear therefore to be less firmly united than singly bound atoms, whereas the reverse might have been expected. Baeyer attempted to explain this peculiarity by his **strain theory.**[1]

From stereochemical considerations Baeyer came to the conclusion that the angle between the valencies of the carbon atom, according to the tetrahedral model (see p. 31), remains unaltered when two carbon atoms are united by a single bond ; but before a double bond can come into being, the respective valencies must be displaced from their original direction by a certain angle. A definite strain is thus set up in the molecule, rendering the multiple bond easily ruptured by suitable reagents to form a compound with single bonds and normally directed valencies. A similar, but even greater strain may be imagined to exist in compounds containing triple bonds. As was pointed out by Baeyer, the internal strain in the case of the polyacetylenes tends to manifest itself in the development of explosive properties.

In the same manner the distortion of the carbon bonds may be calculated for various cyclic compounds. It is found that this is comparatively large in cyclopropane (I), becomes less in cyclobutane (II) and disappears almost entirely in cyclopentane (III). In cyclohexane (IV) the displacement from the normal is somewhat greater than in the 5-membered compound. In qualitative agreement with Baeyer's strain theory it is found that the stability of the ring structure towards reagents increases as we pass from cyclopropane to cyclopentane, which is the most stable of the lower members of the series (see also p. 356 *et seq.*).



Cyclopropane — Cyclobutane — Cyclopentane — Cyclohexane.

[1] See p. 356 for a fuller discussion.

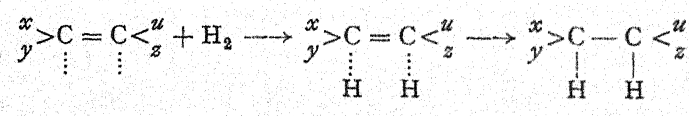
Later a detailed study of unsaturated compounds led to the conclusion that the double bond did not completely utilise the affinity between the two carbon atoms, but left a surplus on each atom which was termed *residual affinity*. These ideas, as developed by Thiele, have aroused great interest and discussion.

Thiele's theory of unsaturated compounds was originally put forward in an attempt to explain the observation of Baeyer and Rupe, that when muconic acid is reduced the first step is the addition of two hydrogen atoms to the extreme ends of the hydrocarbon chain, with the formation of a new double bond in the centre. On further reduction this double

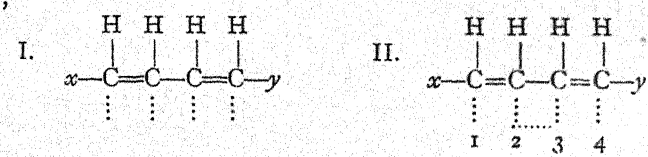
$$\underset{\text{Muconic acid.}}{HOOC{-}CH{=}CH{-}CH{=}CH{-}COOH} \longrightarrow \underset{\text{Dihydromuconic acid.}}{HOOC{-}CH_2{-}CH{=}CH{-}CH_2{-}COOH}$$

bond is also attacked. Similar displacements have been noted by Baeyer [1] in the reduction of benzene carboxylic acids.

Thiele assumed that all such unsaturated compounds contain one or more double bonds, but that the two affinities of a double bond do not completely saturate one another, leaving a certain residual affinity or *partial valency* in excess on each carbon atom. This is illustrated graphically in the following formula, where the dotted lines indicate partial valencies. Addition to this compound follows by each new atom first attaching itself to a partial valency, subsequently taking up the full valency with the simultaneous disappearance of the double bond.



It is supposed that in a system of alternating single and double bonds such as I,



which Thiele describes as **conjugated double bonds,** the two central partial valencies mutually saturate one another, so that addition first occurs at the ends of the system, in the 1, 4 positions (II). As will be explained later, this theory furnishes a good representation of the nature of the benzene ring.

Thiele illustrated the use of his hypothesis by a large number of examples, and it appeared at first to give a satisfactory explanation of the behaviour of many unsaturated organic compounds. In recent years, however, facts have come to light which are not in agreement with the rule of 1 : 4-addition. Thorpe and his co-workers [2] have re-examined the behaviour of butadiene towards bromine and have confirmed the

[1] Baeyer, *Ann.*, 1889, **251**, 271. [2] E. H. Farmer, C. D. Lawrence and J. F. Thorpe *J. C. S.*, 1928, 729. See also Straus, *Ber.*, 1909, **42**, 2872.

simultaneous formation of two primary dibromo-addition products, one of which is a 1 : 2- and the other a 1 : 4-compound, the former being usually in excess. Either of these compounds, on being heated, undergoes rearrangement to give a mixture of the two isomerides containing about 80 per cent. of the 1 : 4-compound, although the isomeric change is very slow at room temperature. Hence the process of addition to such a system is not as simple as is represented in Thiele's theory.

$$CH_2:CH.CH:CH_2 \longrightarrow \begin{cases} BrCH_2.CHBr.CH:CH_2 \\ BrCH_2.\overset{\uparrow\downarrow}{C}H:CH.CH_2Br \end{cases}$$

An investigation[1] of the addition of HBr to butadiene at −80° in the presence of antioxidants (*e.g.* diphenylamine, hydroquinone) shows that about 80-90 per cent. of the 1 : 2-addition product, $CH_2:CH.CHBr.CH_3$, is formed together with 10-20 per cent. of crotyl bromide, $CH_3.CH:CH.CH_2Br$, resulting from 1 : 4-addition. At higher temperatures, however, isomerisation into crotyl bromide occurs, and this is the compound usually isolated.

In a similar manner isoprene, $CH_2:C(CH_3).CH:CH_2$, adds on hydrogen in the presence of platinum black to give in the first instance a mixture of 1 : 2, 1 : 4 and 3 : 4 derivatives,[2] these three reactions proceeding simultaneously. The unsaturated cyclic compounds 1 : 3-cyclohexadiene and 1 : 3-cyclopentadiene also yield considerable proportions of 1 : 2-dibromo-addition products.[3]

A further contribution to the valency problem has been developed in modern times by Werner, who, unlike Thiele, makes no assumption of directed valency bonds, but substitutes the conception of affinity distributed over definite areas of the atomic surface.[4] According to these views, which have been most fruitful in their application to complex inorganic compounds, the valency of a carbon atom varies with the spatial configuration of the atom and its degree of affinity towards adjacent atoms. Compounds of the "first order" are thus built up in which the individual atoms still contain surplus components of affinity, even if the substance is of the type known as saturated. This residual valency can attach other atoms or molecules to form compounds of the "second order" (*e.g.* molecular compounds). But whether we prefer the idea of fixed valency, which has already proved of incalculable value in organic problems, or the conceptions of Werner as developed in the chemistry of the metalloids, the assumption of residual affinity remains indispensable.

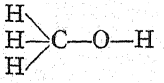
(*e*) Derivation of Structural or Constitutional Formulæ

The constitutional or structural formula is derived from the molecular formula by building up every possible combination of the constituent

[1] M. S. Kharasch, E. T. Margolis and F. R. Mayo, *J. Org. Ch.*, 1937, I, 392; R. Voigt *J. pr. Ch.*, 1938, **151**, 307. [2] S. V. Lebedev and A. O. Yakubchik, *J. C. S.*, **1928**, 823 [3] Farmer and Scott, *J. C. S.*, **1929**, 172. [4] A. Werner, *Neuere Anschauungen auf dem Gebiete der anorganischen Chemie* (1923).

atoms, consistent with the foregoing considerations of valency, and selecting that particular one which agrees best with the properties of the compound.

It is a comparatively simple matter to assign a formula where the number of atoms in the molecule is small. Thus a compound of molecular formula CH_4O must possess the structure given below, if we assume the valencies of C, O and H to be four, two and one respectively. In other cases it may be necessary to make a choice from several alternatives.



The final allocation of a structural formula should be made with reference to the following general considerations, based on laboratory experience :—

1. The possibility of converting the substance into, or of forming it from, compounds of known constitution. In this connection it may be noted that *when compounds undergo double decomposition, the new atom or radical entering into a molecule usually takes up the position occupied by the outgoing atom or radical.*[1] The structure of the radicals exchanged generally remains unaltered during this process.

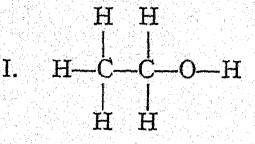
For example, ethyl chloride, C_2H_5Cl, for which there is only one possible constitution, is under certain conditions transformed into alcohol, C_2H_6O, by interaction with water :

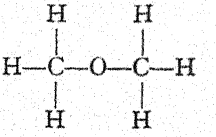
$$C_2H_5Cl + H_2O = C_2H_5OH + HCl.$$

Conversely, ethyl alcohol by treatment with hydrochloric acid regenerates ethyl chloride :

$$C_2H_5OH + HCl = C_2H_5Cl + H_2O.$$

We must therefore assume alcohol to contain the radical C_2H_5- or $CH_3.CH_2-$, already known to exist in ethyl chloride, and consequently also the monovalent hydroxyl group $-OH$. For these reasons alcohol is allotted formula I below,





which is in complete harmony with its chemical behaviour. Of the six hydrogen atoms present, one obviously differs from the other five in its reactivity and the ease with which it is replaced by metals or radicals. Hence this hydrogen atom is assumed to be linked indirectly to carbon through oxygen.

Consideration of these facts leads to the rejection of the only other possible structure II for a substance of molecular formula C_2H_6O. The latter represents methyl ether, which is isomeric with ethyl alcohol. Here the six hydrogen atoms are all seen to be in the same state of combination.

[1] In special cases, to be discussed later, a migration of atoms or radicals may occur.

Formula II may also be derived from the formation of methyl ether by the interaction of sodium methoxide and methyl iodide :

$$H_3C.O.Na+I.CH_3 = H_3C.O.CH_3+NaI.$$

As a further example, the constitution of acetic acid, $C_2H_4O_2$, may be examined. This substance is produced by the oxidation of ethyl alcohol, according to the equation

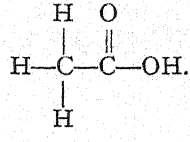
$$C_2H_6O+O_2 = C_2H_4O_2+H_2O.$$

One of the four hydrogen atoms differs in its properties from the other three. It is readily replaced by metals or monovalent radicals and its whole behaviour shows it to be united to oxygen in the form of a hydroxyl group, and not directly attached to carbon.

The first step was therefore to write acetic acid as $C_2H_3O(OH)$, and next to determine the structure of the C_2H_3O radical. This problem was solved by Kekulé, who showed that the three hydrogens must be attached to one and the same carbon atom, since potassium acetate, when heated with potassium hydroxide, yields methane and potassium carbonate.

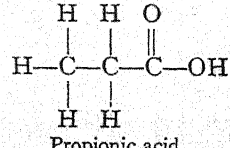
$$\underset{\text{Potassium acetate}}{C_2H_3O(OK)}+KOH = \underset{\text{Methane}}{CH_4}+K_2CO_3.$$

The constitution of acetic acid is therefore assumed to be



It will be seen when we come to deal with the properties of the acid that this formula is in good agreement with its chemical behaviour.

2. *The chemical and physical character of a compound is a function of its molecular structure*, and the chemical similarity of a number of compounds is dependent on the common presence of certain " typical " groups of atoms. Constitution is therefore frequently decided by comparing the physical or chemical properties of the substance with those of a compound of known structure. Every alcohol, for example, contains the hydroxyl group (—OH), and all compounds which show those properties characteristic of the alcohols may also be assumed to contain a hydroxyl group in the molecule.


Propionic acid.

The large majority of organic acids contain the carboxyl group, —COOH, as given above under acetic acid. If then primary propyl alcohol, $CH_3.CH_2.CH_2.OH$, yields on oxidation an acid of the molecular formula $C_3H_6O_2$, the latter probably contains the group —COOH and possesses the structural formula given above.

Intramolecular Rearrangement

As already indicated, the atom or radical entering a molecule by double decomposition occasionally fails to occupy the position of the out-going atom or radical, more particularly if the reaction takes place at a high temperature.

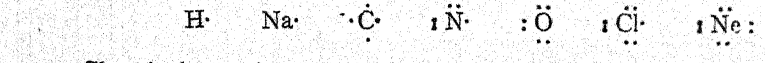
Hence some uncertainty attaches to a constitutional formula deduced by any single one of the methods described under I. The result can only be regarded as probable when derived from the consideration of several different reactions, each of which leads to the same conclusion.

In general, a structural formula is only accepted as established beyond doubt when it has been confirmed by synthesis.

The Electronic Theory of Valency [1]

Great advances have been made in our conception of valency by interpreting it in the light of the electronic theory, according to which atoms are built up solely of *protons* and *electrons*. A *proton* is a unit of positive electricity having extremely small dimensions and a mass of 1·007 (O = 16). An *electron*, or unit of negative electricity, is of considerably greater dimensions than a proton but only about 1/1840 of its mass. Atoms, then, being externally neutral bodies, are composed of equal numbers of protons and electrons. All of the protons, with about half of the electrons, are packed closely together into a small space constituting the atomic *nucleus*. The remainder of the electrons, the number of which gives the *atomic number* of the atom, are in rapid rotation in orbits around the nucleus and hence occupy a much greater volume than the latter. These planetary electrons arrange themselves in layers round the nucleus, each layer containing a definite number corresponding to the condition of maximum electrical stability. The chemist, however, is concerned almost exclusively with the outermost layer, since the chemical properties of the atom, including that of valency, depend almost entirely on the number and disposition of the electrons in the *outer shell*, which is therefore termed the *valency shell*.

Except for the transition elements in group 8 and the rare gases in group O, the number of electrons in the valency shell corresponds to the number of the group into which the element falls in the periodic scheme. Thus hydrogen and the alkali metals, Na,K, etc., in the first group have only one valency electron, carbon in the fourth group has four, nitrogen has five, oxygen six, and chlorine seven. In the rare gases, from neon upwards, there is a complete outer group of eight electrons. These atoms can be represented diagrammatically as follows :—



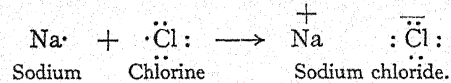
Chemical reactions are supposed to occur owing to the tendency of

[1] For detailed treatment see G. N. Lewis on *Valence*; Sidgwick, *The Electronic Theory of Valency* (Churchill, 1927).

valency shells to assume a more stable arrangement. For the majority of the common elements stability is reached when there is an outer shell of eight electrons (an *octet*); for hydrogen and the rare gas helium, however, the stable number is two. In the case of elements of groups I and II, possessing one and two valency electrons respectively, the stable condition may be attained by the complete loss of these electrons. This change occurs on ionization and results in the exposure of the underlying shell of electrons, which is already in its most stable arrangement. Elements of group VII, on the other hand, may readily complete their octets by gaining or even sharing an electron from another atom. In the rare gases the valency shell exists in a formation of maximum stability, hence these elements have no chemical reactivity whatever.

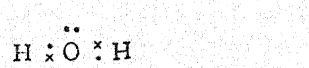
Actual combination between two atoms may be supposed to occur in one of two ways, both of which were suggested by Lewis.

1. Union may take place by an atom completely transferring one or more of its electrons to another atom. As atoms are externally neutral groups of protons and electrons, this leaves the first atom positively and the second negatively charged. Combination of this type is found chiefly among salts of acids and bases, and is known as **electrovalency.** The oppositely charged ions may be regarded as separate entities, normally held together by electrostatic attraction. The equation given below illustrates the electronic changes which take place when sodium and chlorine combine to give sodium chloride. In order to make these and the following formulæ clearer, the electrons belonging to different atoms are in some cases indicated by different signs.

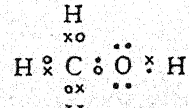


Sodium Chlorine Sodium chloride.

2. A type of valency which is of much more frequent occurrence in organic compounds is that of **covalency.** In this case the two atoms unite by holding a pair of electrons in common, one being contributed by each atom. For example, the oxygen atom in water has increased its sextet to an octet by acquiring a share in two other valency electrons from the atoms to which it is linked. At the same time each hydrogen atom has attained a stable shell of two by sharing an oxygen electron. In methyl alcohol the four electrons in the outer shell of the carbon atom are raised to eight by sharing with three hydrogen electrons and one oxygen electron. Each pair of shared electrons constitutes a non-ionizing



Water

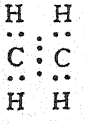


Methyl alcohol.

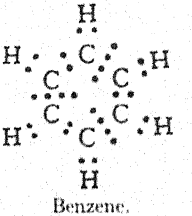
bond as commonly pictured in organic formulæ. For simplicity of representation the electrons are figured as static; but it must be

remembered that they are in reality supposed to be in a state of rapid motion.

The ordinary *double bond*, as in C=C or C=O, is regarded as a double co-valency, *i.e.* as four electrons shared between two atoms, two electrons being supplied by each. A double bond of this type is symmetrical in structure, and has a plane of symmetry containing the double linking.



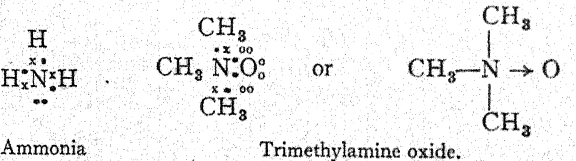
Ethylene



Benzene.

3. Another and more recently proposed form of co-valency, the development of which is chiefly due to Lowry and to Sidgwick, is that in which *one* of the atoms supplies *both* of the electrons required for the union. Lowry and Sugden term this type of bond a *semi-polar double bond* (see below), and Sidgwick refers to it as a *co-ordinate link*. This mode of union was first applied to certain inorganic compounds by Lewis.

In order that combination of this kind may be possible, one of the atoms (the *donor*) must have at least two valency electrons (termed a *lone pair*) which are not concerned in union with any other part of the molecule, and the other atom (the *acceptor*) must be able to take up two electrons to form a more stable arrangement.[1] Many atoms, even when in the combined state, possess one or more of these lone pairs of electrons. Oxygen in water has two and nitrogen in ammonia or organic bases has one. Under suitable conditions, therefore, O and N in these compounds may function as *donor atoms*. Atomic oxygen, on the other hand, has a valency shell of six electrons (two less than the stable arrangement) and may play the part of an *acceptor atom*. Thus in trimethylamine oxide, $(CH_3)_3NO$, the two nitrogen electrons which were unattached in trimethylamine are supposed to be shared with the oxygen. Sidgwick represents this kind of linking by a short arrow, *e.g.* N→O. The single line indicates that it is a link formed by the sharing of two electrons, and the direction of the arrow shows that both the electrons are provided by the nitrogen atom.



Ammonia

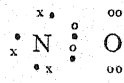
Trimethylamine oxide.

An arrangement such as this necessarily implies that the molecule has developed polarity. The nitrogen atom becomes positively charged

[1] Sidgwick, *The Electronic Theory of Valency*, p. 116.

owing to two of its electrons being less in its proximity than previous to the union, and the oxygen atom becomes negatively charged, having two additional electrons in its outer shell. Lowry, who first proposed the above electronic formula for the amine oxides,[1] therefore describes the linking between N and O as a **semi-polar double bond**, since it appears to possess the combined properties of a co-valence and an electrovalence. It must be emphasised, however, that later investigations of the physical properties of such compounds do not support the earlier assumption that the charge on the oxygen atom is equivalent to the complete transfer of an electron from nitrogen to oxygen.[2]

If the older formulation of the amine oxides, $(CH_3)_3N : O$, which assumes the presence of a normal double bond, is translated into the electronic formula, the nitrogen atom must be represented as having a valency shell of ten electrons. Such an arrangement is unstable. The new formulation, on the other hand, preserves the octet, which is the stable arrangement for nitrogen.



Similarly it has been suggested that in order to preserve the octet a nitro group should be formulated with one double bond and one of the semi-polar type. Measurements of dipole moments have shown, however, that the electronic states of the two oxygen atoms are identical. This is now explained on the theory of **resonance** or **mesomerism.** In its original form this assumed that the molecule oscillated rapidly between the two states $\left(N\overset{O}{\underset{O}{\rightleftharpoons}}N\overset{O}{\underset{O}{\rightleftharpoons}}\right)$; it is now regarded as having an intermediate structure which is not capable of being represented by our present symbols (see p. 88).[3]

From the foregoing pages it will be seen that the usual formulæ of the organic chemist are readily translated into electronic formulæ by replacing each single non-ionizing bond by a pair of shared electrons; each ionizing bond by the transfer of an electron; and each double bond by four shared electrons, except in cases where a co-ordinate link or semi-polar double bond is known to be present.

II.—STEREOCHEMISTRY[4]

Whereas the theory of structure treats only of the sequence and manner in which the atoms are linked together within the molecule, stereochemistry concerns itself with those chemical phenomena which are directly attributable to the *configuration*, or disposition of the atoms

[1] Lowry, *Trans. Faraday Soc.*, 1923, **18**, 285. [2] Compare R. F. Hunter and R. Samuel, *Chem. and Ind.*, 1935, **54**, 31, 635. [3] See Sidgwick, *Ann. Rep. Chem. Soc.*, **1934**, 37. [4] See K. Freudenberg, *Stereochemie* (1933); T. M. Lowry, *Optical Rotatory Power* (1935); G. Wittig, *Stereochemie* (1930); Hantzsch, *Grundrisz der Stereochemie*, 2nd edition, Leipzig, 1904; Werner, *Lehrbuch der Stereochemie*, Jena, 1904. P. Walden, *Fünfzig Jahre Stereochemischer Lehre und Forschung*, Ber., 1925, **58**, 237.

in space. That type of isomerism which involves substances of the same constitution, but different configuration, is called **stereoisomerism**, and the substances are known as *stereoisomerides*.

From the historical point of view stereochemistry has developed logically from the theory of structure. At first it was found possible to explain the number and properties of almost all compounds of similar molecular formula by assuming a difference of constitution. One by one, however, cases of isomerism were discovered which could not be explained on the ground of structural dissimilarity, and these were for a time classed as "physically isomeric substances," without any reason being assigned for the isomerism.

Stimulated by the work of Pasteur and Wislicenus,[1] a stereochemical theory of the isomerism of optically active compounds was developed independently and almost simultaneously in 1874 by van't Hoff[2] and Le Bel. Since then many investigators have made valuable contributions to this subject and none more so than Emil Fischer in his brilliant researches on the sugars.

The stereochemistry of nitrogen has similarly been advanced by the work of Hantzsch and Werner, Le Bel, Pope and Peachy, Wedekind, Mills and others.

1. Stereochemistry of Carbon

According to their behaviour the stereoisomeric carbon compounds may be divided into two groups as follows :—

A. Substances which are identical in all their chief properties, but differ in their "optical activity" or action on polarised light, when examined in the fused state or in solution. Such compounds are termed **optical isomerides, optical antipodes** or **enantiomorphs,** and with few exceptions contain within the molecule at least one *asymmetric carbon atom* (*cf.* footnote 1, p. 33). By this term is understood a carbon atom whose four valencies are united to four *different* monovalent atoms or groups.

B. Substances which, having the same structural formula, differ in all their physical and many of their chemical properties, but exert no influence on polarised light. These are compounds containing double or triple bonds, and are generally described shortly as **geometrical isomerides.** Many of the saturated cyclic compounds also exhibit this kind of isomerism. (See cyclohexane series, p. 469.)

In their original publications van't Hoff and Le Bel showed that both of these types of isomerism could be explained on the assumption that the valency bonds were arranged in three dimensions around the carbon atom.

[1] Wislicenus, *Ann.* 1873, 167, 343. [2] Van't Hoff, *The Arrangement of Atoms in Space*, translated by A. Eiloart (Longmans).

A. Optical Isomerism

According to van't Hoff's fundamental hypothesis of stereochemistry, the four valency bonds of the carbon atom are imagined to be directed towards the summits of a regular tetrahedron, at the centre of which lies the atom itself. It is easily seen by reference to figures 3 and 4 [1]

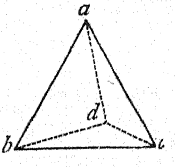


Fig. 3.

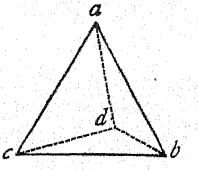


Fig. 4.

that a substance of the type C *a b c d*, in which *a*, *b*, *c* and *d* are four different atoms or groups, can assume two different configurations which are not superimposable. A carbon atom such as this is described as asymmetric.

One configuration is a mirror-image of the other, and the difference between them is comparable with that existing between the right hand and the left. This *enantiomorphism* or mirror-image relationship of the molecules is repeated in the optical and crystallographic properties of the substances ; but in most remaining physical and chemical properties the compounds are identical. Structural figures such as 3 and 4, expressing the spatial arrangement of the atoms, are called space formulæ, and illustrate the fact that *the molecule of an optically active compound possesses no plane of symmetry*.

In studying stereochemical problems it is advisable not only to visualise the space formulæ indirectly on the plane of the paper, but also directly by use of space models as devised by Kekulé, van't Hoff and others. The simplest type of model is that in which the four valency bonds are represented by four pieces of rubber tubing, connected together at one end, and directed towards the corners of a regular tetrahedron. Coloured balls attached to the tubes by rods represent the different groups.

Van't Hoff's theory of the carbon atom is supported by Bragg's X-ray analysis of the structure of the diamond,[2] in which the carbon atoms are found to be united by tetrahedrally directed valency bonds.

In its main essentials Le Bel's theory agrees with that of van't Hoff. Le Bel, however, makes no assumption regarding the geometrical arrangement of the valency bonds in space. He states that molecular asymmetry will necessarily exist if the four different radicals are arranged in space around the carbon atom, whatever may be the geometrical form of the molecule. In this respect van't Hoff's ideas accord more closely with later developments of stereochemistry.

[1] For the sake of clearness the carbon atom, which is supposed to lie at the centre of the tetrahedron with its bonds directed towards *a*, *b*, *c* and *d*, is omitted in the space formulæ. The letters *a*, *b*, *c*, *d* represent the four different atoms or radicals attached to the asymmetric atom.

[2] W. H. Bragg, *Proc. Roy. Soc.*, 1913, 89 A, 277.

Certain inorganic substances (*e.g.* sodium chlorate) are optically active in the crystalline state. This is due to the *molecules* being arranged in an asymmetric manner within the crystal and the activity therefore disappears when the crystal passes into solution. The optical activity of carbon and other compounds in solution is a consequence of the asymmetric arrangement of the *atoms* in the molecule. In some cases the crystals of such compounds also possess optical activity.

Compounds containing one Asymmetric Carbon Atom

As already indicated, the most striking difference between isomers containing an asymmetric carbon atom lies in their optical activity in the liquid or dissolved state. To every active compound rotating the plane of polarisation through a certain angle in a given direction, there corresponds an isomeride which, otherwise identical in properties, rotates the plane of polarised light to the same extent in the opposite direction.

The two enantiomorphs differ only in sign of rotation, and are therefore termed *optical antipodes*. They are distinguished arbitrarily as dextrorotatory and laevorotatory modifications, or more commonly by prefixing the letters *d*- and *l*- (or + and −) to the name of the substance, *e.g.* *d*- and *l*-lactic acids.

If equimolecular quantities of the *d*- and *l*- forms of a compound are mixed with one another, a product is obtained in which all optical activity disappears, owing to the mutual or *external compensation* of the two constituents. Inactive products of this type are called *racemic compounds* or *mixtures*[1] and are usually distinguished by the prefix *r*- or *dl*-. When crystalline they are frequently definite compounds having double the molecular weight of the *d*- or *l*- forms. In the fluid state or in solution racemic compounds exist as a mixture of the *r*- form in equilibrium with equivalent amounts of the *d*- and *l*- modifications, thus recalling the behaviour of double salts.[2] By methods to be described later it is possible to resolve these racemic compounds into their active components.

A few rare cases have been observed, notably in the camphor series, in which no definite compound is produced, but the two optical enantiomorphs form mixed crystals with one another, the product being termed a *pseudoracemic mixture*.[3]

A typical instance of a compound containing an asymmetric carbon atom is lactic acid, $H_3C.CH(OH).COOH$, which occurs in two optically

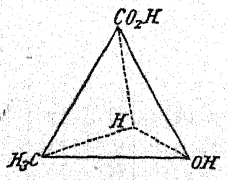


FIG. 5.

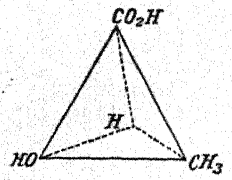


FIG. 6.

[1] The name is derived from racemic acid, the first representative of this class to be observed.

[2] Racemic compounds are not necessarily *completely* dissociated into the *d*- and *l*- forms in solution. Cotton has shown that on mixing equimolecular solutions of copper *d*- and *l*-tartrates, dissolved in alkali, the colour at once deepens, thus indicating compound formation (*Ann. Chim. Phys.*, 1896, **8**, 347; *Trans. Faraday Soc.*, 1930, 377).

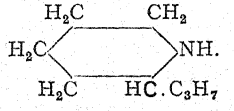
[3] See Pope and Read, *J. C. S.*, 1913, **103**, 1515.

active modifications and an optically inactive or racemic form. The two optical antipodes are related to one another in the manner shown in Figs. 5 and 6.

The following additional examples may be mentioned, in which the asymmetric atom is indicated by heavier type :

Malic acid, $COOH.\mathbf{C}H(OH).CH_2.COOH$
Asparagine, $COOH.\mathbf{C}H(NH_2).CH_2.CONH_2$
Mandelic acid, $C_6H_5.\mathbf{C}H(OH).COOH$
Chloro-bromo-fluoro-acetic acid, $(ClBrF)\mathbf{C}.COOH$

Coniine,



Each of these compounds is known in two optically active forms and an inactive racemic form.

It can readily be demonstrated that the existence of these isomerides, like the property of optical activity itself, is dependent on molecular asymmetry. With the destruction of the asymmetry of the carbon atom—for example, when a molecule of the formula C *a b c d* is converted into C *a b* c_2—both optical activity and isomerism disappear.[1] Thus the reduction of either of the optically active malic acids, $HOOC.CH_2.\mathbf{C}H(OH).COOH$, leads to the formation of the same inactive succinic acid, $HOOC.CH_2.CH_2.COOH$.

Compounds with two or more Asymmetric Carbon Atoms

As the number of asymmetric carbon atoms in a compound becomes greater, the number of possible isomerides increases rapidly. *In general, a compound of unsymmetrical structure containing* n *asymmetric carbon atoms can exist in* 2^n *optically active isomerides*, made up of a number of pairs of mirror-image forms possessing equal and opposite rotations. This general statement postulates a structural dissimilarity between the asymmetric atoms involved ; if this is not the case, and the molecule is symmetrically built, certain of the asymmetric atoms will be structurally alike and consequently some of the possibilities of isomerism will vanish.

It is only feasible at this stage to discuss the isomerism dependent on the presence of two asymmetric atoms within the molecule. Examples of greater complexity, such as those offered in the sugar series, will be examined later under their respective headings.

As already stated above, compounds containing two dissimilar asymmetric carbon atoms are capable of existing in 2^2, or four, optical isomerides, made up of two pairs possessing equal and opposite rotatory powers ; to these must be added the two (inactive) racemic forms. This can be deduced in a simple manner by distinguishing the two atoms by

[1] Those compounds which contain an asymmetric carbon atom form a special class in which the spatial arrangement of the atoms within the molecule is such that no plane of symmetry is present. Such compounds must occur in two modifications, the space formulæ of which are mirror-images of one another. As Pasteur first recognised, they are distinguished by enantiomorphous crystal structure and optical activity of contrary sign.

the letters A and B, and their different spatial configurations by the signs + and —. We have then the following active compounds :

1.	2.	3.	4.
+ A	— A	+ A	— A
+ B	— B	— B	+ B

An example of this type is dibromo-cinnamic acid,

$$C_6H_5.CHBr.CHBr.COOH,$$

which is known to occur in four active as well as two racemic forms.

Compounds possessing two asymmetric but structurally similar carbon atoms, of the general formula $C_{abc}—C_{abc}$, exist in three different configurations, two of which are optically active antipodes ; the other is represented by an internally compensated structure and cannot be resolved into active components (see p. 37). In addition, the two active enantiomorphs may unite to produce a racemic form.

The different modifications can be derived in a manner similar to that shown above, by placing A = B, in which case configurations 3 and 4 become identical.

1.	2.	3.
+ A	— A	+ A
+ A	— A	— A

The substance represented by 3 is optically inactive, despite the presence of two asymmetric complexes, owing to the activity of the one group being equal and opposite to that of the other. In other words, it is *internally compensated.* Compounds of this type are also described as *i-* or *meso-* forms. This inactive and non-resolvable form cannot occur in cases where there is only one asymmetric atom present in the molecule, and is to be distinguished carefully from the inactive, *externally compensated*, racemic type which by special methods can be resolved or separated into its optically active components.

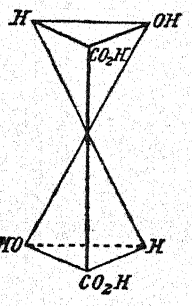


FIG. 7.

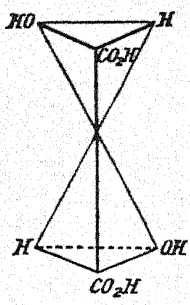


FIG. 8.

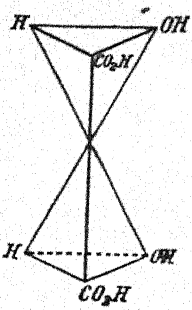
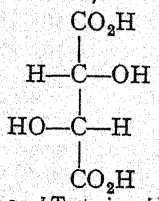
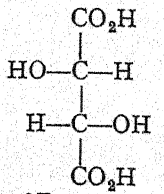


FIG. 9.

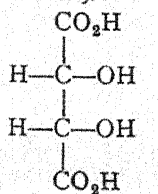


1. *d*-Tartaric acid



2. *l*-Tartaric acid

4. *dl*-Tartaric acid, *r*-tartaric or racemic acid



3. *i*-Tartaric acid or meso-tartaric acid.

One of the best known examples of isomeric compounds containing two similar asymmetric atoms is found in the dihydroxy-succinic acids, HOOC.CHOH.CHOH.COOH, which have played a conspicuous part in the history of optical activity. In accordance with theory, these exist as dextro-, laevo-, and *i*- or meso-tartaric acids; and in addition as racemic acid, which has double the molecular weight of the above three forms, and is produced by union of *d*- and *l*-tartaric acids. The dextro- and laevo-acids are optical antipodes, whereas meso-tartaric and racemic acids are inactive. As shown in the formulæ at bottom of previous page, racemic acid is resolvable and meso-tartaric acid non-resolvable. The lack of optical activity in meso-tartaric acid is also revealed by the fact that the molecular formula (see Fig. 9) possesses a *plane of symmetry*, *i.e.* a plane dividing the structure into two halves bearing the relationship of object to mirror-image.

Racemisation

It should be noted that many optically active compounds become more or less completely inactive under the influence of heat or chemical reagents, a process known as *racemisation*. In this way *d*-tartaric acid when strongly heated with water is transformed into a mixture of racemic and meso-tartaric acids.

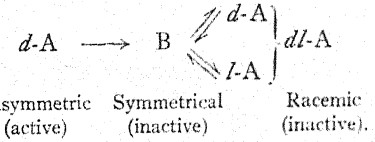
A number of other acids such as aspartic, mandelic and camphoric acids may be converted into their racemic forms in a similar way. Some compounds (limonene, pinene, amyl alcohol) lose their activity on being merely heated to a sufficiently high temperature; others (tartaric acid, mandelic acid, amyl alcohol and many amino-acids) are slowly racemised when heated with aqueous alkalis; in still other cases (limonene, *d*-valeric acid) sulphuric acid is an active catalyst.

In a few instances the optical activity has been found to disappear spontaneously in the course of time at the ordinary temperature. Walden discovered that esters of optically active bromo-succinic and phenyl-bromacetic acids gradually became inactive during the lapse of several years. This was formerly described as a case of *autoracemisation*. It has since been shown, however, that no racemisation occurs in these esters if they are completely freed from traces of hydrobromic acid.[1] Genuine examples of autoracemisation will be found in 2 : 2′-dibromodiphenyl-4 : 4′-dicarboxylic acid (p. 43) and the oxime of 2-hydroxy-1-acetyl-3-naphthoic acid (*β*-form, p. 59).

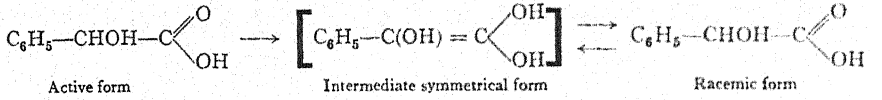
Racemisation appears to be due to the occurrence of some kind of molecular change under the influence of heat or a suitable catalyst, as the result of which an asymmetric molecule A exists temporarily in equilibrium with an isomeric form B (or a simple derivative thereof) which is not asymmetric in structure. The optically active (say, *d*-rotatory) compound A is therefore undergoing constant conversion into the inactive

[1] R. Kuhn and T. Wagner-Jauregg, *Naturwissenschaft*, 1929, 17, 103.

substance B. The molecules of A regenerated from B by the equilibrium process will, however, be composed of an equal mixture of *d*- and *l*-rotatory



forms, since in general there is no reason why one mirror-image isomeride should be produced in excess of the other. In the end, therefore, the whole of the active form A is converted into the racemic compound *dl*-A. *d*-Mandelic acid, for example, loses its activity when heated for several hours with a large excess of aqueous alkali, a change which may occur according to the scheme [1]



On the other hand, many optically active acids which might be expected to undergo this molecular rearrangement retain their activity undiminished under such conditions.

A remarkably effective reagent for investigating the ease of racemisation of carboxylic esters, acid amides and ketones of the general formula R′R″CH.CO.R has been discovered by McKenzie in sodium or potassium ethoxide. The process is a *catalytic* one and systematic studies have been carried out [2] by examining the changes, if any, which occur when a small amount of an alcoholic solution of the reagent is added to a solution of the active substance in alcohol. In many cases this leads to complete racemisation within a short time even at room temperature; in others the optical rotation either changes more slowly or not at all. From the theoretical standpoint every optically active compound of the above general formula may be considered to be capable of undergoing racemisation by existing in equilibrium with the tautomeric form R′R″C : C(OH).R. It has been established by McKenzie, however, that two conditions must be fulfilled before this change can occur in practice. Firstly, as is implied in the above formulæ, the asymmetric atom must be attached to a hydrogen atom and be situated in the α-position to a ketonic group. Secondly, racemisation only takes place if an aromatic group such as phenyl or naphthyl is also united directly to the asymmetric atom. Thus phenyl-*p*-tolylacetic ester, $\begin{matrix} C_6H_5 \\ CH_3.C_6H_4 \end{matrix}\!\!>\!CH.COOR$, undergoes rapid racemisation, whereas purely aliphatic acids and esters of corresponding structure retain their activity even on vigorous treatment

[1] For a discussion of similar cases see Lowry, *B. A. Rep.*, 1904, 211. [2] A. McKenzie, *J. C. S.*, 1915, **107**, 704; 1919, **115**, 602. Wren, *ibid.*, 1918, **113**, 210. A. McKenzie and Miss I. A. Smith, *Ber.*, 1925, **58**, 894.

with alkalis. Two other esters which are optically stable in the presence of sodium ethoxide are atrolactic ester, $\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C(OH).COOR$ and β-phenylbutyric ester, $\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!CH.CH_2.COOR$; the former because there is no labile hydrogen atom attached to the asymmetric atom, and the latter because the asymmetric atom is situated in the β-position, so that even if a hydrogen atom in the α-position does migrate it can do so without destroying the asymmetry of the molecule. Similarly, if the phenyl radical in mandelic ester is removed from immediate contact with the α-carbon atom or replaced by an alkyl group, as in the following lactic derivatives, the resulting compounds are not racemised by alcoholic alkali, although they still retain in the α-position an asymmetric atom attached to hydrogen.

$C_6H_5.CH_2.\overset{\displaystyle OH}{\overset{|}{C}}\overset{\displaystyle H}{\overset{|}{.}}COOR$	$CH_3.\overset{\displaystyle OH}{\overset{|}{C}}\overset{\displaystyle H}{\overset{|}{.}}COOR$
β-Phenyl-lactic ester	Lactic ester.

The same considerations have been found to apply to certain other classes of optically active compounds. Although secondary aliphatic alcohols of the type R.CHOH.R′, in which there is no possibility of a tautomeric change of the above nature, are known to be stable to alkalis, McKenzie has shown that *l*-benzoin readily loses its rotatory power in the presence of a trace of alcoholic potash. Inactivation in the latter case may occur by the intermediate formation of stilbenediol.

$$\underset{\text{Asymmetric}}{C_6H_5.CHOH.CO.C_6H_5} \rightleftharpoons \underset{\text{Symmetrical.}}{C_6H_5.C(OH)=C(OH).C_6H_5}$$

The interconversion (*epimerisation*) of acids of the sugar series when heated with quinoline is a racemisation process affecting the α-carbon atom and may be explained in the same manner (see p. 294).

Resolution of Racemic Compounds

Compounds containing asymmetric carbon atoms, which have been prepared synthetically by methods not involving the use of any active substance, are never found to possess optical activity. They generally conform to the racemic type, since in such a synthesis there are always produced equimolecular amounts of the dextro- and laevo-rotatory forms. On the other hand, asymmetric compounds produced with the mediation of living organisms are almost invariably active.[1]

[1] If a chemical synthesis is effected with the intermediate aid of an optically active substance which is subsequently removed, the product may on occasion also exhibit activity. By means of such *asymmetric syntheses* (p. 47), it is possible to imitate the processes of the living agency.

Notwithstanding modern research, the methods originally introduced by Pasteur for the resolution of racemic compounds into their optically active components have undergone comparatively little extension. The following are the methods at present available for this purpose.

(a) *Mechanical Separation of the Crystals.*—In a few instances it is possible, by allowing a solution of the racemic mixture to crystallise under certain conditions, to obtain the two enantiomorphs depositing individually—provided they do not form mixed crystals. If, in addition, the crystals possess characteristic differences of the nature of hemihedral facets or striations, it may be possible to separate them by hand.

This method has a very limited application,[1] since the crystallisation of mechanically separable enantiomorphous forms has been observed in very few cases. It was first utilised by Pasteur in 1848 to resolve racemic acid. On crystallising the sodium ammonium salt of racemic acid at a temperature below 27°, it deposits in the form of the corresponding salts of dextro- and laevo-tartaric acids, *d*- and *l*-$NaNH_4C_4H_4O_6+4H_2O$; the crystals have different hemihedral facets and may be separated from one another by hand. If the crystallisation is allowed to take place at a temperature above 27°, the *transition temperature*, there separates out unchanged sodium ammonium racemate $(NaNH_4C_4H_4O_6+H_2O)_2$.

A modification of this method has been devised by Ostromisslensky,[2] who showed that supersaturated solutions of the *dl*-compounds, on seeding out with a substance which is isomorphous with the desired active form, can be made to deposit that form exclusively, the other remaining in solution. The success of this method of separation is entirely independent of the presence of an asymmetric carbon atom in the substance with which the solution is seeded. Optically active asparagine, for example, may be precipitated from a supersaturated solution of *dl*-asparagine by the addition of a crystal of glycine, which is itself inactive.

(b) *Resolution by the Biochemical Method.*—This second method of Pasteur is based on the discovery that when lower organisms, such as bacteria, fungi or yeasts, are allowed to grow in a solution containing a racemic compound, the two enantiomorphs are destroyed at different rates (selectively assimilated), so that an excess of one of the active forms accumulates in the solution.[3] Thus Pasteur found that when *penicillium glaucum* was cultivated in a solution of ammonium racemate, the *d*-tartrate was preferentially destroyed, leaving a solution containing an excess of ammonium *l*-tartrate. In actual practice this method is only of use in comparatively few cases.

(c) *Resolution by Means of Salt Formation.*—This method depends on the following principle. When a racemic acid A is combined with an optically active, *e.g.* laevorotatory, base B, two salts are formed, namely (*l*-B, *l*-A) and (*l*-B, *d*-A). As may readily be seen by reference

[1] For the resolution of lactic acid by this means see Purdie, *J. C. S.*, 1893, **63**, 1143. [2] Ostromisslensky, *Ber.*, 1908, **41**, 3035. [3] A relationship therefore exists between physiological activity and the configuration of chemical compounds. Emil Fischer has shown the influence of configuration on the ability of the monosaccharides to undergo alcoholic fermentation (*Ber.*, 1894, **27**, 2035) and on the enzymatic hydrolysis of glucosides. Optical antipodes frequently differ in their action on the animal organism. *l*-Nicotine, for example, is more poisonous than its enantiomorph (Pictet and Rotschy, *Ber.*, 1904, **37**, 1233). See also index under "molecular configuration and physiological activity."

to space models, these salts are not enantiomorphous forms, being produced by combination of the same laevo-base with acids of opposite rotation. In general, therefore, they will possess different solubilities and may be separated by fractional crystallisation. From the individual salts it is then possible to obtain the two active acids. For example, if a solution of racemic acid be saturated with the optically active base cinchonicine, the first salt to crystallise out is cinchonicine *l*-tartrate; on the other hand, by employing the base quinicine the salt of the *d*-acid is the first to separate. Similarly by union with an active acid, a racemic base may be resolved into its *d*- and *l*-forms. The method may be extended to the resolution of any racemic compound which will unite with acids or bases. In this manner the great majority of resolutions have been effected.

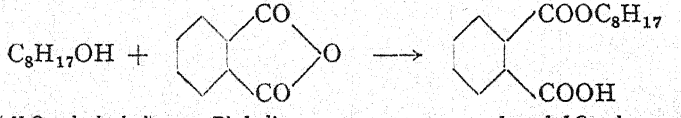
In certain cases a complication arises owing to the *r*-acid combining, for example, with a *d*-base to form the salt (*d*-base, *r*-acid) in addition to the more usual mixture of (*d*-base, *d*-acid) and (*d*-base, *l*-acid). A salt of the first type is termed a **partially racemic compound** (*Ladenburg*).

(d) *Other Resolutions by Means of Active Substances.*—The two components of a racemic acid have been shown by Marckwald and McKenzie [1] to esterify at different rates with the same active alcohol. Employing an excess of the racemic acid, the unesterified acid at the end of the reaction was found to be optically active. When, for example, *r*-mandelic acid is incompletely esterified with *l*-menthol, the uncombined residual acid is laevorotatory.

Optically active substances appear in general to react with perceptibly different velocities with the *d*- and *l*-forms of a compound, particularly when the course of the reaction depends in high degree on the constitution of the reagents. A reaction of this type is amide formation, which has also been applied to the resolution of racemic compounds.[2]

Another recent method of resolution is that put forward almost simultaneously by Erlenmeyer, jun.,[3] and Neuberg.[4] According to Erlenmeyer, a racemic base may be resolved by bringing it into reaction with an active aldehyde. In this way active condensation products termed anils are formed, which are separable by fractional crystallisation. The active base may then be regenerated from the anil by hydrolysis with acids.

Racemic alcohols have been resolved by Pickard and Kenyon [5] by combining them with the anhydride of a strong dibasic acid (succinic or phthalic acid) to form acid esters. For example,



(*dl*-Octyl alcohol) Phthalic anhydride *d*- and *l*-Octyl hydrogen phthalates.

[1] Marckwald and McKenzie, *Ber.*, 1901, **34**, 469. [2] Marckwald and Meth, *Ber*, 1905, **38**, 801. [3] Erlenmeyer, jun., *Ann.*, 1904, **337**, 307. [4] Neuberg, *Ber.*, 1903, **36**, 1192 **38**, 868. [5] Pickard and Kenyon, *J. C. S.*, 1911, **99**, 45.

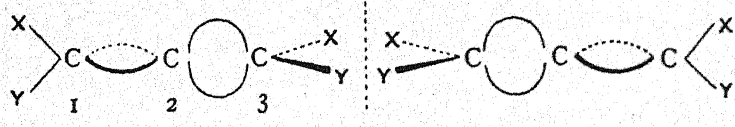
The racemic acid esters (*e.g.* octyl hydrogen phthalates) thus obtained are monobasic acids and can be resolved by use of an alkaloid, usually brucine, after which the individual *d*- and *l*-esters can be hydrolysed to give the optically active alcohols.

Partial resolutions on a micro scale have been effected in one or two isolated cases by taking advantage of the different adsorption coefficients of the *d*- and *l*-components of a racemate for an optically active adsorbent. Thus *dl*-*p*-phenylene-bisiminocamphor was partly resolved by Rule and Henderson [1] by adsorbing it from a petroleum-benzene solution on the upper part of a large tube filled with *d*-lactose. The adsorbed layer was then washed with the solvent until it had expanded to fill the tube (compare chromatographic analysis, p. 98). *p*-Phenylene-bisiminocamphor recovered from the upper part of the tube was dextrorotatory, $[\alpha]_{5461}+485°$ (in $CHCl_3$), whereas that from the lower part was laevorotatory, $[\alpha]_{5461}-728°$. The pure active compound has $[\alpha]_{5461}\pm 1975°$. Similar results were obtained by Karagunis and Coumoulos [2] using the racemic chromium complex, $[Cr(en)_3]Cl_3$, on powdered active quartz.

Conditions for Enantiomorphism

A general condition for the occurrence of a compound in optically active forms is that the molecule should exist in two mirror-image structures which cannot be superimposed one upon the other. In order that this condition may be fulfilled, *it is not essential for the molecule to contain an asymmetric atom* in the strict sense of the definition given on p. 32. A compound possesses the possibility of existing in enantiomorphous forms provided [3] that the configuration of the molecule is devoid of (1) a plane of symmetry, (2) a centre of symmetry and (3) an alternating axis of symmetry.

Plane of Symmetry.—As has already been stated, the space formula of a compound containing an asymmetric carbon atom is without any plane of symmetry. A simple example of a substance containing no asymmetric atom, but for which it is possible to build up two mirror-image and non-superimposable structures, is furnished by allene derivatives of the following type.

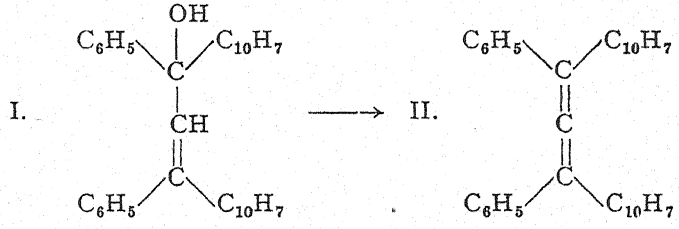


If we imagine the terminal group XYC (1) to be in the plane of the paper, then owing to the tetrahedral arrangement of the carbon valencies we must represent the double bond between (1) and (2) as lying in a plane at right angles to that of the paper. The bond between (2) and (3) will then be in the plane of the paper, leaving X and Y (3) disposed, for example, with X behind and Y in front of the plane. As a result of

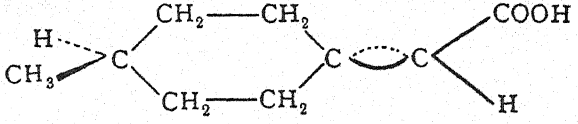
[1] *Nature*, 1938, **141**, 917. *J. C. S.*, 1939, 1568. [2] *Nature*, 1938, **142**, 162. See also Tsuchida, Kobayashi and Nakamura, *Bull. Soc. Japan*, 1936, ii, 38. [3] See T. V. Barker and J. E. Marsh, *J. C. S.*, 1913, **103**, 837.

this *spiro*-arrangement (see also *spiro-compounds*, p. 50) the structure possesses no plane of symmetry and cannot be superimposed upon its mirror-image.

Although van't Hoff predicted that compounds of this type should exist in optically active forms, it is only within quite recent times that the possibility has been demonstrated experimentally. In 1935 Mills and Maitland [1] dehydrated the inactive alcohol of formula I by various reagents to give a racemic phenyl naphthyl allene II, which melted at 242° to 244°. Dehydration by means of *d*-camphor sulphonic acid, on the other hand, led to the isolation of a strongly dextrorotatory $\alpha\gamma$-diphenyl-$\alpha\gamma$-di-1-naphthyl allene, m.p. 159°, the corresponding laevo-rotatory isomeride of the same melting-point being obtained by use of *l*-camphor sulphonic acid.



The first successful resolution of a compound containing no asymmetric atom was accomplished by Perkin, Pope and Wallach [2] (1909) in the case of 1-methyl-cyclohexylidene-4-acetic acid. By recrystallising the

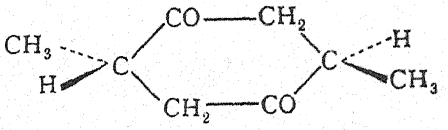


brucine salts of this acid from aqueous alcohol it was separated into two active components. Here also the molecular formula has no plane of symmetry, and two non-superposable mirror-image structures may be built up.

Centre of Symmetry.—Interesting examples of a new class of inactive and indivisible compounds were discovered among the *trans*-diketo-hexamethylenes (Ladenburg) and the *trans*-diketo-piperazines (Fischer). If in the annexed formula we assume the 6-membered rings to lie in the plane of the paper, then the similar *trans*-substituents (*e.g.* CH_3) must be disposed one behind and one in front of this plane. These compounds each possess two similar asymmetric atoms, but are not of the true meso type since there is no plane of symmetry. Nevertheless, experiment has

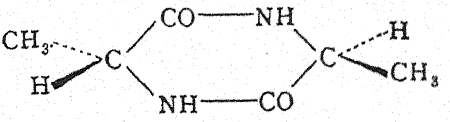
[1] W. H. Mills and P. Maitland, *Nature*, 1935, 135, 994; *J. C. S.*, 1936, 987. See, however, P. Maitland, *Ann. Rep. Ch. Soc.*, 1939, 239. For the resolution of a carboxylic acid of allene type see E. P. Kohler, J. T. Walker and M. Tishler, *J. A. C. S.*, 1935, 57, 1743. [2] *J. C. S.*, 1909, 95, 1789.

shown that compounds of this kind cannot be resolved into active components. The real criterion of asymmetry is the configuration of the



Trans-Dimethyl-diketohexamethylene.

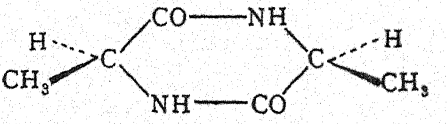
molecule as a whole, and not the relationship existing between two or more atoms within the molecule. *On building up the mirror-image of one of the above structures it will be found to be identical with the original ;*



Trans-Dimethyl-diketopiperazine (alanyl anhydride).

there is therefore no possibility of optical isomerism. A close inspection of the formulæ shows that a line drawn from any atom or group to a point in the middle of the ring will, if produced further, meet a similar atom or group. Such a point is known as a *centre of symmetry.*

The existence of a centre of symmetry is therefore sufficient to destroy the possibility of optical isomerism. Ladenburg described the case of *trans*-dimethyl-diketohexamethylene as one of pseudo-symmetry.



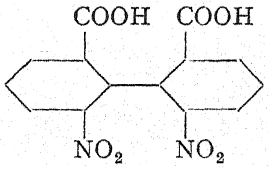
Cis-Dimethyl-diketopiperazine.

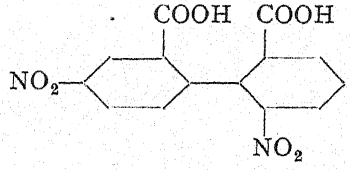
In the *cis*-compounds of the above types there is neither a plane nor a centre of symmetry. The *cis*-diketo-piperazines have been found to occur in optically active forms.

Alternating Axis of Symmetry.—Compounds possessing an alternating axis of symmetry are such that on rotating any atom or group round the axis through an angle of 90°, it will, on being reflected across the horizontal plane perpendicular to the axis, come into superposition with a corresponding atom or group. This condition also holds for every successive rotation of 90°. In such cases similar atoms or groups alternate above and below the plane of reflection and the molecule can be superimposed on its mirror-image. This type of symmetry is rarely met with. It occurs, for example, among certain substituted cyclobutane derivatives, in which the alternating axis of symmetry is perpendicular to the plane of the ring and the latter corresponds to the plane of reflection. (For examples see Barker and Marsh, *loc. cit.*)

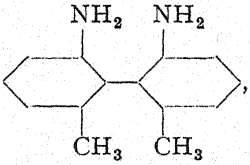
Optical Isomerism due to Restricted Rotation about a Single Bond[1]

Optical isomerism of a new kind has recently been found to exist in the diphenyl series (p. 499). This development arose from the discovery of Christie and Kenner that it was possible to resolve substituted diphenic acids, such as the 6 : 6′- and 4 : 6′-dinitro-derivatives (I and II) into their optical isomerides.

I. 

II. 

Since then a number of substituted diphenic acids have been resolved,[2] and others shown to be incapable of resolution. Meisenheimer[3] has extended the work to basic derivatives such as 6 : 6′-diamino-*o*-ditolyl,



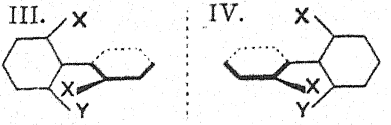
, which also exists in enantiomorphous forms.

At first it was believed to be an essential condition for optical isomerism in the diphenyl series that at least three of the four positions adjacent to the bond joining the two benzene nuclei should be occupied by substituents. Later, the resolution of certain di-ortho-substituted compounds such as diphenyl 2 : 2′-disulphonic acid[4] and 2 : 2′-diiodo-diphenyl-4 : 4′-dicarboxylic acid proved that only two *o*-substituents were necessary, provided they were sufficiently large. Compounds of this type, however, are comparatively easily racemised by heating, and the ease of racemisation increases when iodine in the above acid is replaced by the smaller substituent bromine. The corresponding dichloro-compound has not yet been resolved.[5]

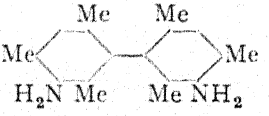
An explanation of this type of isomerism has been suggested in the theory of restricted rotation, which was advanced independently by[6] Turner and Le Fevre, Bell and Kenyon, and Mills. It is supposed that the free rotation of the benzene nuclei round the bond uniting them is restricted or altogether prevented by the presence of the substituents in the ortho-positions. If free rotation is inhibited, it is then possible to

[1] For a general survey see R. Adams and H. C. Yuan, *Chem. Rev.*, 1933, **12**, 261. [2] Christie and Kenner, *J. C. S.*, 1922, **121**, 614; Christie, Holderness and Kenner, *J. C. S.*, 1926, 671. McAllister and Kenner, *J. C. S.*, 1928, 1913; F. Bell and J. Kenyon, *Chem. and Ind.*, 1926, 45, 864. [3] *Ber.*, 1927, **60**, B, 1245. [4] Miss M. S. Lesslie and E. E. Turner, *J. C. S.*, 1932, 2394. [5] N. E. Searle and R. Adams, *J. A. C. S.*, 1933, **55**, 1649; 1934, **56**, 2112. [6] Turner and Le Fevre, *Chem. and Ind.*, 1926, 45, 831; Mills, *ibid.*, 883, 905. Bell and Kenyon, *ibid.*, 864.

build up two non-superimposable mirror-image forms for each of the above compounds (*e.g.* III and IV).



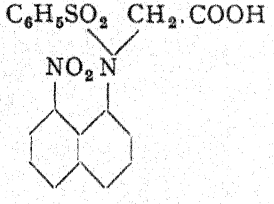
The probability of this explanation becomes evident when actual space models of these derivatives are examined. It is then seen that the benzene nuclei are interlocked. The actual nature of the force preventing rotation is still an open question ; it may be a purely mechanical obstruction or electropolar forces may be involved. But the success of Moyer and Adams [1] in resolving 3 : 3′-diamino-dimesityl, in which the four ortho groups are identical and practically non-polar, supports the theory of mechanical blocking. The same conclusion is indicated by the fact that the series Br>Cl>O—>F represents not only the relative blocking powers of the substituents but also their relative atomic diameters.



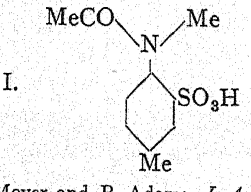
All attempts to resolve compounds such as 4 : 4′-dinitro-diphenic acid and 3 : 3′-dichloro-diphenyl-5 : 5′-dicarboxylic acid have resulted in failure. In these cases the requisite *o*-substituents are missing.

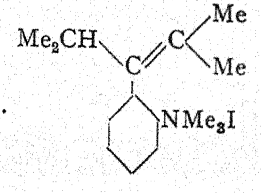
The case of 6 : 6′-dinitro-diphenic acid illustrates the fact that complete asymmetry is not an essential condition for optical isomerism, since the compound occurs in two non-superposable forms. As in many other cases, the molecular structure of this compound possesses certain elements of symmetry and is therefore described as *dissymmetric* rather than asymmetric.

Optical isomerism due to restricted rotation round a single bond would be expected to occur in other compounds besides the diphenyl group. Further support for the theory was furnished by Mills and Elliot [2] in resolving the benzene sulphonyl derivative of 8-nitro-1-naphthyl glycine. In this case the optical isomerides are unstable, and the rotatory power disappears in the course of a few hours (autoracemisation). In the absence of the nitro group no isomerism occurs.



Still more recently, simple benzene derivatives exhibiting optical activity of this type have been discovered by Mills and co-workers in the compounds I and II.



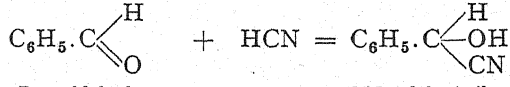


[1] W. W. Moyer and R. Adams, *J. A. C. S.*, 1929, 51, 630. [2] Mills and Elliot, *J. C. S.*, 1928, 1291. See also Meisenheimer, *Ber.*, 1927, 60, B, 1245.

Compound I was found to undergo slow racemisation,[1] the activity of the sodium salt falling to zero over a period of some hours. If the sulphonic group is replaced by the less bulky carboxyl group, however, no resolution can be effected. The active iodides of structure II showed great optical stability,[2] but here also all optical isomerism disappeared when hydrogen was substituted for one of the relatively bulky methyl groups ($C{=}CMe_2 \longrightarrow C{=}CHMe$).

Asymmetric Synthesis

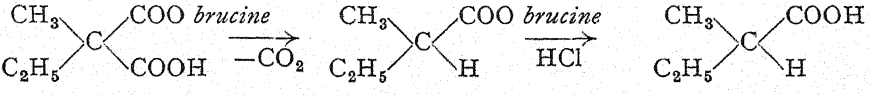
It has already been stated that when a symmetrical compound is converted by ordinary chemical reaction into one of asymmetric type, the new product is not optically active but is of the racemic variety, *e.g.*



Benzaldehyde *dl*-Mandelonitrile.

The ordinary chemical and physical properties of the optical isomerides (*e.g.* the *d*- and *l*-mandelonitriles in the above equation) are identical and there is no reason why the one form should be produced in greater amount than the other. If, however, such a reaction is carried out under the influence of an optically active grouping which is subsequently removed, the product may be found to exhibit optical activity. A synthesis of this kind is termed an *asymmetric synthesis*.

Marckwald [3] in 1904 claimed to have effected the first asymmetric synthesis by preparing an active *l*-valeric acid from the acid brucine salt of methyl ethyl malonic acid, by heating the latter at 170°. The



actual mechanism by which active valeric acid is formed in these reactions has been the subject of discussion. Recent work supports the view that the process is not a true asymmetric synthesis, but that the activity of the final product depends on the fact that the deposition of the crystalline acid brucine salt (which contains a newly created asymmetric C-atom in the malonic residue) is accompanied by a displacement of the equilibrium of the two diastereoisomerides in accordance with their differing solubilities. Thus the solid salt before decomposition by heat does not contain brucine hydrogen *d*-methyl-ethylmalonate and brucine hydrogen *l*-methylethyl-malonate in equal amounts.

In the same year A. McKenzie prepared a laevorotatory atrolactic acid by treating *l*-menthyl benzoylformate with one molecular proportion

[1] Mills and R. M. Kelham, *J. C. S.*, 1937, 274. [2] Mills and G. H. Dazeley, *ibid.*, 1939, 460. For another example of simple type see R. Adams and L. J. Dankert, *J. A. C. S.*, 1940, 62, 2191. [3] *Ber.*, 1904, 37, 349, 1368.

of methyl magnesium iodide,[1] and subsequently removing the menthyl grouping by hydrolysis.

$$C_6H_5.CO.COOR \longrightarrow C_6H_5.\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\dot{C}}}.COOR \longrightarrow C_6H_5.\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\dot{C}}}.COOH$$

Benzoyl formic ester — Atrolactic acid.

The following asymmetric syntheses are also due to McKenzie and his co-workers.

When an ester of pyruvic acid is reduced, it is converted into a lactic ester, with the simultaneous creation of an asymmetric atom. By reducing *l*-menthyl or *l*-bornyl pyruvates in an aqueous solvent with aluminium amalgam, McKenzie obtained lactic esters which on hydrolysis gave a lactic acid containing an excess of *l*-acid. Similarly the *d*-amyl ester led to the formation of an excess of *d*-lactic acid,[2]

$$\underset{\text{Pyruvic ester}}{CH_3.CO.COOR} \longrightarrow \underset{\text{Lactic ester}}{CH_3.CHOH.COOR} \longrightarrow \underset{\text{Lactic acid.}}{CH_3.CHOH.COOH}$$

A further asymmetric synthesis effected by McKenzie and Wren is based on the oxidation of fumaric acid to racemic acid by means of potassium permanganate.[3] The oxidation of *l*-bornyl fumarate produced

$$\begin{matrix} CH.COOR \\ \| \\ CH.COOR \end{matrix} \longrightarrow \begin{matrix} CHOH.COOR \\ | \\ CHOH.COOR \end{matrix}$$

a mixture of *d*- and *l*-tartaric esters containing an excess of bornyl *l*-tartrate, and on removing the bornyl group a laevorotatory tartaric acid was obtained. By using *d*-bornyl fumarate an excess of *d*-tartaric acid was formed.

Rosenthaler [4] showed that the combination of aldehydes with hydrogen cyanide in the presence of enzymes gives rise to active cyanhydrins. Benzaldehyde and HCN in the presence of emulsin yield optically active *d*-mandelonitrile, which on hydrolysis gives an active *l*-mandelic acid. Similar results were obtained by Bredig and Fiske,[5] who used optically active alkaloids in place of enzymes. Quinine for example gives a laevorotatory mandelonitrile and quinidine a dextro-rotatory product.

Many attempts have been made to produce optically active substances by generating asymmetric compounds under the influence of circularly polarised light or an asymmetric arrangement of polarised light and magnetic field. The former method was suggested independently by Le Bel and van't Hoff and has recently been realised experimentally. Karagunis [6] states that triarylmethyls containing three different groups attached to the central carbon atom (CR′R″R‴) combine with bromine

[1] McKenzie and co-workers, *J. C. S.*, 1904, **85**, 1249. See also 1906, **89**, 365, 688. [2] *J. C. S.*, 1905, **87**, 1373; 1909, **95**, 544, 1105. [3] *J. C. S.*, 1907, **91**, 1215. It may be noted that maleic acid on oxidation yields mesotartaric acid. [4] *Biochem. Zeit.*, 1909, **14**, 238; **17**, 257; **19**, 186. [5] *Biochem. Zeit.*, 1912, **46**, 7. [6] Karagunis and Drikos, C., 1936, i. 3298.

or chlorine under the influence of *d*-circularly polarised light to form very weakly laevorotatory triarylmethyl halides. With *l*-circularly polarised light the rotation is dextrorotatory.

Asymmetric Decomposition

A somewhat different procedure has been advocated by Cotton, who discovered that copper *d*- and *l*-tartrates in alkaline solution exhibit circular dichroism, a *d*-circularly polarised ray, for example, being more strongly absorbed by the *d*-salt than by the *l*-compound (*Cotton effect*). Hence Cotton tried to decompose a solution of the racemate with *d*-circularly polarised light in the hope of obtaining a mixture containing an excess of *l*-tartrate. No activity could be observed, however. After many fruitless attempts along these lines on the part of various investigators, success has finally been achieved by Werner Kuhn,[1] and S. Mitchell.[2] Kuhn made use of *dl*-α-azidopropionic dimethylamide, $CH_3.CHN_3.CO.N(CH_3)_2$. This was found to have an absorption band due to the azido-group, situated in the ultra-violet region at $\lambda = 2900$ Å.U., in the neighbourhood of which the rotation rose enormously. On passing *d*-circularly polarised light of the same order of wavelength (chiefly $\lambda = 3135$) through the solution, decomposition ensued with the liberation of nitrogen, the recovered dimethylamide having the rotation, $\alpha_{5780} = +0{\cdot}78°$ ($l = 1$). When *l*-circularly polarised light was employed the product had $\alpha_{5780} = -1{\cdot}04°$.

The asymmetric photochemical decomposition of humulene nitrosite effected by Mitchell has the merit of simplicity, since it was brought about by the use of visible light in the red part of the spectrum (6000—7800 Å.U.), and the change could be followed throughout by polarimetric readings. Humulene is an inactive sesquiterpene which combines with nitrous anhydride to form a racemic nitrosite. A solution of the latter in ethyl butyrate on being irradiated with *l*-circularly polarised light of the above wavelength showed a gradually increasing *d*-rotation (maximum value $\alpha_{5780} = +0{\cdot}30°$) which eventually fell during the course of sixty-four hours to zero, by which time the decomposition of the nitrosite was complete. Similar rotations of the opposite sign were obtained in a parallel experiment with *d*-circularly polarised light.

These syntheses of active compounds from racemic material are not asymmetric syntheses in the usual sense of the word but are akin to Pasteur's resolutions with bacteria or moulds, which feed preferentially on one of the active forms in a solution of the racemate.

The causes which first led to the formation of optically active compounds in nature have been the subject of much speculation. The successful photochemical decompositions outlined above indicate one possible solution of the problem, since ordinary daylight is well known

[1] W. Kuhn and E. Knopf, *Zeit. phys. Chem.*, 1930, B, 7 (4), 292. [2] S. Mitchell, *J. C. S.*, 1930, 1829.

to contain under certain conditions a small proportion of circularly polarised light.[1] But whatever the original source of the activity, it is probable that the great majority of highly active substances now elaborated by animal and vegetable organisms are formed by asymmetric syntheses under the influence of optically active enzymes or other products (alkaloids, carbohydrates, etc.) already present in the organism.

B. Geometrical Isomerism

The tetrahedra representing two carbon atoms united by a single bond are in contact at one point only, and capable of independent rotation about their common axis. If this were not so, even the simplest compound of this type, such as ethane, $H_3C—CH_3$, should exist in innumerable modifications. There is, however, only one ethane known. Stereoisomerism is therefore not possible with ethane derivatives unless the carbon atom is asymmetric. As suggested by Wislicenus, it is probable that the atoms or groups united to the two carbon atoms exert a mutual directive influence on each other, until by rotation about the common axis the whole system is transformed into the most stable configuration.

The case is otherwise with doubly bound carbon atoms as contained in ethylene derivatives of the general formula *a b* C : C *c d*. All independent turning of the tetrahedra ceases here, since two corners of each are in union, with a whole edge in contact and the remaining four valency bonds lying fixed in one plane.

For this reason compounds of the formula a b C : C *a b* (*and also of the general structure a b* C : C *c d*) *exist in two stereoisomeric forms*, corresponding to the configurations :

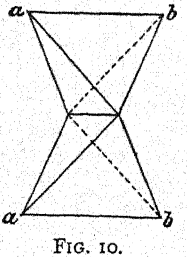


Fig. 10.

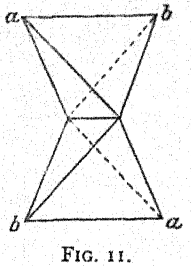


Fig. 11.

By projection on to a plane parallel to that containing the four radicals, these formulæ may be simplified to

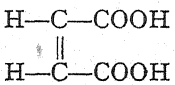
I. $a—C—b$ / $a—C—b$ and II. $a—C—b$ / $b—C—a$

Compounds of configuration I, in which similar groups lie on the same side of the molecule, are known as *cis*-forms ; they possess one

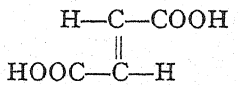
[1] Byk maintains that ordinary diffused daylight contains a small preponderance of one form of circularly polarised light (*Zeit. phys. Chem.*, 1904, **49**, 662).

plane of symmetry perpendicular to the axis of the double bond, and another containing C, *a*, *b* and the double bond. Those of configuration II, with similar groups on opposite sides, and having one plane of symmetry containing the axis of the double bond are known as *trans*-forms.

The best known illustration of this type of isomerism is furnished by maleic and fumaric acids :



Maleic acid



Fumaric acid.

In maleic acid the two carboxyl groups lie on the same side of the molecule (*maleinoid* position), and in fumaric acid on opposite sides (*fumaroid* position). The compounds differ not only in physical but also in chemical behaviour (see p. 277). Maleic acid, for example, owing to the proximity of the carboxyl groups, readily forms a stable anhydride, a change not possible in the case of fumaric acid. When strongly heated, fumaric acid is partially transformed into water and the anhydride of maleic acid.

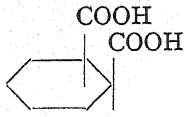
Geometrical isomerism is a common occurrence among those ethylene derivatives in which two different groups are united to each doubly bound carbon atom. Into this class fall the two dimethyl-ethylenes, $CH_3.CH:CH.CH_3$, crotonic and isocrotonic acids, $H_3C.CH{:}CH.COOH$, angelic and tiglic acids, $CH_3.CH{:}C(CH_3).COOH$ and many others.

Under certain conditions the geometrical isomers of the ethylene series are interconvertible ; thus by heating maleic acid in aqueous solution with a small amount of hydrochloric acid, it is converted into fumaric acid.

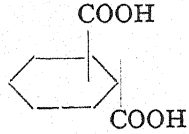
A similar geometrical isomerism is found among the cyclic polymethylene compounds, despite their saturated character. In this case, the closed structure of the ring inhibits axial rotation of the carbon atoms in the same manner as the double bond of ethylene derivatives.[1] A comparatively large number of isomerides of this class is known, including the hexahydroterephthalic acids,[2] and the quinitols, $C_6H_{10}(OH)_2$. The existence of isomerism is explained in the same way by assuming that certain groups in the compound may occupy opposing positions in space, in the sense that they may in one case be in proximity, and in the other be removed from one another. A foundation for this explanation is provided by the fact that the one isomer frequently undergoes intramolecular reactions which appear to necessitate neighbouring positions of the groups involved, whereas the other isomer does not undergo these reactions at all. The two hexahydrophthalic acids, for example, exhibit

[1] It is also possible to consider ethylene as the simplest example of a molecule with ring structure. [2] Baeyer, *Ann.*, 1888, **245**, 103 ; 1889, **251**, 257 ; 1890, **256**, 1, **258**, 1, 145 ; 1891, **266**, 169 ; 1892, **269**, 145.

the same relationship as maleic and fumaric acids, as indicated in the following diagrams. The *cis*-acid readily forms an anhydride; whereas the *trans*-anhydride, which is only obtained with difficulty, is converted on fusion into the stable *cis*-anhydride. This change involves a rearrangement of the groups.



Maleinoid or *cis*-acid.

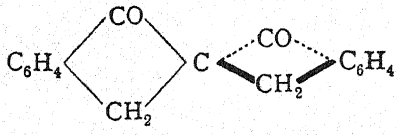


Fumaroid or *trans*-acid.

Spirocompounds

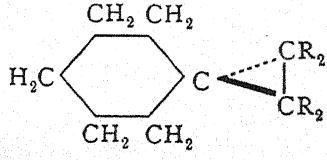
Closely related to the allene derivatives mentioned on p. 40 are the **spirans** or **spiro-compounds.**[1] Spirans are cyclic compounds built up of at least two homo- or hetero-cyclic rings, and having one ring-atom common to both cyclic structures (I and II). Owing to the tetrahedral arrangement of the bonds around the common atom,[2] the two rings may be regarded as occupying planes at right angles to each other. In many cases the spatial disposition of the groups leads to the occurrence of stereoisomerism.

I.



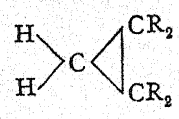
Bis-1-hydrindone-2 : 2-spiran.

II.

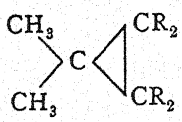


An extensive investigation has been carried out by Thorpe, Ingold and co-workers on the formation and stability of spiro-compounds.[3] It is well known that in cyclopropane the distortion of the valency bonds from the normal is so great that derivatives of this hydrocarbon are not readily formed and are unstable. The above authors have shown that the ease of formation of the cyclopropane ring is increased when the CH_2

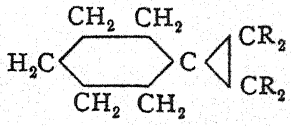
I.



II.



III.

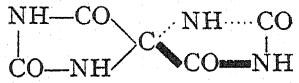


group in I is replaced by the *gem*-dimethyl group as in II and to a still greater degree by the cyclohexane group as in the spiro-compound III. It is therefore concluded that in the simple cyclopropane ring (in which the bonds are calculated to enclose an angle of 60°, as compared with the normal value of 109°28′ for methane) the strain between the carbon bonds is lessened by the introduction of the bulky *gem*-dimethyl group, $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C$, or the cyclohexane residue. In the last two cases the widening of the angle

[1] A number of these compounds have been prepared by Leuchs and co-workers, *Ber.*, 1912, 45, 189, 2114 and later. [2] This holds for N as well as C; compare stereochemistry of nitrogen, p. 54. [3] *J. C. S.*, 1915, 1080; 1919, 320; 1920, 1579; 1921, 1199; 1922, 1496, 1821; 1923, 122, 3140; 1925, 1678; 1926, 2011.

between two of the bonds by space-filling groups may be assumed to bring about a decrease in the angle enclosed by the remaining two bonds, thus facilitating the closure of the ring. Once it is formed, the ring in these last-named compounds is under less strain and hence is less liable to disruption.

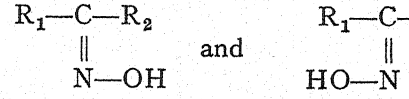
The resolution of *spiro*-5 : 5-hydantoin by Pope and Whitworth [1] furnishes a remarkably simple example of an optically active spiran.



2. Stereochemistry of Nitrogen

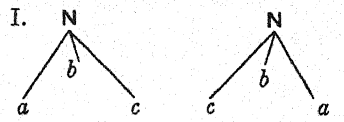
(a) *Optical Isomerism*

The frequent occurrence of oximes and hydrazones, all of which contain the group $>C:N-$, in geometrically isomeric forms, has been explained by Hantzsch on the assumption that the nitrogen and carbon atoms lie in the same plane as the double bond joining them, with the third nitrogen valency lying outside this plane. Oximes, for example, may theoretically be written as



and in many cases both forms have been isolated (see pp. 56 *et seq.*).

If the three nitrogen valencies were arranged in this way in tervalent nitrogen compounds of the type N*abc*, the latter would be expected to occur in optical isomerides as in I. Many attempts have been made to resolve such compounds but without success. For example, no resolution could be effected in the case of benzyl ethyl amine,[2] β-benzyl-hydroxylamine,[3] methylaniline,[4] tetrahydroquinoline,[4] or hippuric acid [5] by means of active acids.



It has therefore been concluded that these compounds N*abc* do not occur in stable enantiomorphous forms. The fact that ammonia and similar compounds have a definite dipole moment (see p. 82) proves that the three radicals *a*, *b* and *c* do not lie in the same plane as the nitrogen atom. The system is therefore assumed to possess a mobility which brings about rapid racemisation (contrast sulphur compounds, p. 61).

(b) *Optically Active Ammonium Salts*

Corresponding to the asymmetric atom of carbon we have that of pentavalent nitrogen, the five bonds of which are united to different atoms or groups. A configuration of this type is represented by the

[1] Sir W. J. Pope and J. B. Whitworth, *Chem. and Ind.*, 1930, **49**, 748. [2] Krafft, *Ber.*, 1890, **23**, 2780. [3] Behrend and König, *Ann.*, 1891, **263**, 175. [4] Ladenburg, *Ber.*, 1893, **26**, 864. [5] E. Fischer, *Ber.*, 1899, **32**, 2470.

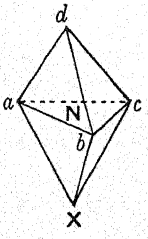
substituted ammonium salts N(a, b, c, d)X, which would therefore be expected to exist in two optically active forms of equal and opposite rotation, and an inactive racemic form containing equimolecular amounts of these two isomers.

In confirmation of this, Le Bel [1] obtained methyl-ethyl-propyl-isobutyl ammonium chloride, $N(CH_3)(C_2H_5)(C_3H_7)(C_4H_9)Cl$, in a feebly active state by submitting a solution of the salt to the action of the mould *penicillium glaucum*. Pope and Peachey [2] prepared the *benzyl-phenyl-allyl-methyl ammonium salt* of *d*-camphorsulphonic acid, and by fractional crystallisation from the non-hydrolysing solvents ethyl acetate and acetone succeeded in resolving it into its enantiomorphous forms. The individual *d*-camphorsulphonates, on treatment with potassium iodide, gave the sparingly soluble substituted ammonium iodides of $[\alpha]_D = +52{\cdot}5°$ and $[\alpha]_D = -51{\cdot}4°$ respectively. These were the first optically pure compounds to be prepared, the activity of which was due to an element other than carbon.

These ammonium bromides and iodides are easily racemised, not only in aqueous or alcoholic solution, but also when allowed to stand in chloroform solution (*autoracemisation*). This is supposed to be due to the dissociation of a molecule of alkyl halide followed by recombination in a different manner.

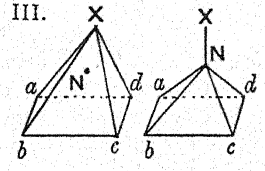
Earlier work on the isomerism of nitrogen compounds led to the consideration of two space arrangements for the pentavalent nitrogen atom. In one of these, due to Willgerodt, the five bonds were assumed to lie at the points of a figure obtained by placing two tetrahedra base to base (II). The nitrogen atom was supposed to lie inside the common triangular base, $a\ b\ c$, with Na, Nb and Nc representing the valencies of the original trivalent nitrogen. Willgerodt's arrangement was subsequently abandoned because it permits a far greater number of isomerides than is actually found in practice, viz., two different optically inactive isomerides Na_3bX, three isomerides Na_2bcX (one of which should be resolvable) and four resolvable forms of N$abcd$X.

II.



The second formula for ammonium compounds, due to Bischoff, represented the N-atom as lying inside a square pyramid X$abcd$ (III), with four valencies directed towards the points of the square base and the ionising valency towards the apex. This also requires a greater number of isomerides than has been observed. For example, compounds of the type N$abcc$X should exist in two forms, one of them resolvable (IV) and the other non-resolvable (V). Similarly, N$abcd$X should occur in three resolvable forms.

III.

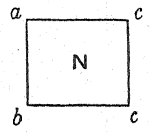


The experimental evidence on which the formulæ have to be judged

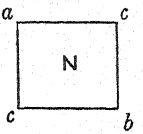
[1] Le Bel, *C. r.*, 1891, **112**, 724. [2] Pope and Peachey, *J. C. S.*, 1899, **75**, 1127.

is somewhat conflicting. There are many cases of dimorphism among these salts and in a number of instances supposed isomers have been shown later to be identical. The main facts may be summarised as follows. No optical isomerism has been observed in compounds of the types Na_3bX or Na_2bcX. Compounds of the type $Nabcd$X occur in a single resolvable form, and the same racemic compound is produced whatever the order in which the radicals *a*, *b*, *c*, *d* are introduced into the molecule.

IV.

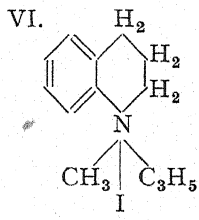


V.



As further examples of the large number of compounds $Nabcd$X resolved by Pope, Wedekind, H. O. Jones and others, may be mentioned those built up of phenyl, methyl, benzyl and a series of alkyl radicals,[1] and the cyclic compound, allyl kairolinium iodide (VI).[2]

VI.



For some years the Bischoff formula was considered to be in best agreement with the experimental facts. Later it became recognised that *the fifth or ionisable valency of nitrogen has no fixed direction with respect to the rest of the atom and is therefore without influence on the asymmetry.* This was first expressed by Werner,[3] who formulated ammonium salts with the ionisable group occupying an outer zone and the four radicals in an inner zone. Werner suggested that the stereochemistry of nitrogen thus resembled that of methane, one atom being present in a positively charged ammonium ion and the other in an electrically neutral molecule.[4]

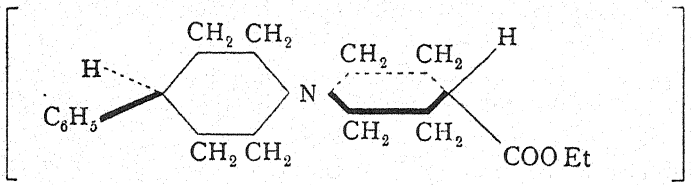
According to modern views the two ions of an ammonium salt are regarded as separate entities, normally held together by the electrostatic attraction of oppositely charged bodies. The individuality of the ions appears to be maintained even in the solid state. Wyckoff,[5] from the X-ray examination of crystals of ammonium chloride, concludes that they are built up of an aggregate of alternating ammonium and chloride ions.

An interesting decision in favour of the tetrahedral as against the pyramidal formula for the ammonium ion has been obtained by the success of Mills and Warren [6] in resolving the following spiro-compound (see p. 54) into its optical isomerides.

The formation of this compound from 4-phenyl piperidine and αε-dibromopentane-γ-carboxylic ester took place very readily, and it

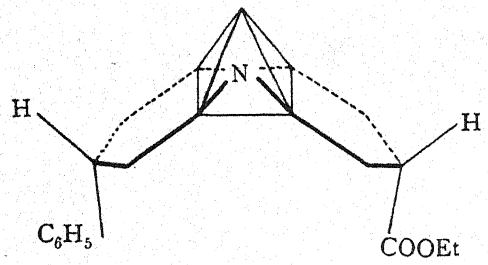
[1] Jones and co-workers, *J. C. S.*, 1906, **89**, 208; 1908, **93**, 295. [2] Buckney, *J. C. S.*, 1907, **91**, 1821. [3] *Zeit. angew. Chem.*, 1906, **19**, 1352. New Ideas on Inorganic Chemistry, p. 53. [4] See also H. O. Jones and Dunlop, *J. C. S.*, 1912, **101**, 1751. Neogi, *J. Amer. Chem. Soc.*, 1919, **41**, 622. [5] *Amer. J. Sci.*, 1922, 3, 177; 4, 473. [6] *J. C. S.*, 1925, **127**, 2507.

is therefore assumed that the valency bonds of the nitrogen atom are

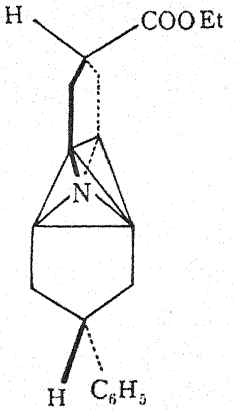


4-Phenyl-4′-carbethoxy-*bis*-piperidinium-1 : 1′-spiran-bromide.

disposed normally and are not under strain. If the arrangement of the N-bonds is tetrahedral, as indicated in the above formula, then the

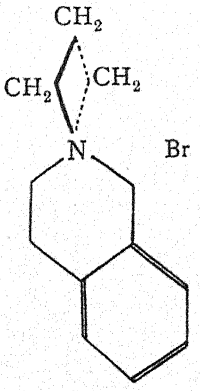


Pyramidal formula.



Tetrahedral formula.

compound is asymmetric, because the two rings must lie in planes perpendicular to one another, thus bringing the terminal substituents, C_6H_5, H and COOEt, H also into planes at right angles to one another. On the Bischoff formula, on the other hand, the compound is symmetrical since in this case the terminal groups lie in one plane which is at right angles to the planes of the two similar rings. The resolution was effected by recrystallising the *d*-bromo-camphorsulphonates from acetone.



The tetrahedral arrangement of the nitrogen valencies also explains the failure of other workers to resolve compounds such as the trimethylene tetrahydro-isoquinolinium salts.[1] On the tetrahedral arrangement the plane containing the isoquinoline rings will cut the trimethylene group at right angles, dividing it into two equal halves and thus constituting a plane of symmetry, as may be seen from the foregoing figure. On the pyramidal formula of Bischoff the compound is asymmetric in structure and should be resolvable.

[1] Jones and Dunlop, *J. C. S.*, 1903, **83**, 1400.

The Inequality of the Five Valencies of Nitrogen

It has been shown by Meisenheimer[1] that the pentavalent nitrogen compound methyl-ethyl-aniline oxide $(CH_3)(C_2H_5)(C_6H_5)N{=}O$, which is prepared by treating the amine with hydrogen peroxide, exists in two optically active forms, despite the apparently identical state of combination of two of the nitrogen bonds. Similar isomerism is exhibited by methyl-ethyl-β-naphthylamine oxide and by kairoline oxide, a cyclic amine oxide.

We may therefore assume that all amine oxides, N*abc*(: O), containing a nitrogen-oxygen double bond and three different alkyl radicals attached to the nitrogen are capable of existing in two enantiomorphous forms, although, as indicated by the experiments of Jones, similar compounds of the type N*aabc*X or N(: *a*)*bc*X in which the double bond lies between nitrogen and carbon cannot be resolved into active isomerides. This was explained by assuming that in the latter compounds the valencies of the double bond, or those united to the two similar radicals, are incapable of binding ionisable groups, whereas in the amine oxides the valency formerly bound to the ionisable acidic group participates with one of the four remaining valencies in the double bond. A fundamental assumption of this theory is the inequality of the five nitrogen valencies in ammonium compounds, it being supposed that the fifth bond, uniting ionisable groups, was of a different nature. The probability of this hypothesis was strengthened by the discovery of Meisenheimer that in compounds of the type $(CH_3)_3NCl_2$, or $(CH_3)_3N(OH)_2$, the chlorine atoms or hydroxyl groups are in different states of combination. For example, two different substances of the formula $(CH_3)_3N(OH)(OCH_3)$ are produced according as a salt of trimethylamine oxide is treated with sodium methoxide (I) or the addition compound of trimethylamine oxide with methyl iodide is decomposed by sodium hydroxide (II).

$$\text{I. } (CH_3)_3N{:}O \longrightarrow (CH_3)_3N{<}^{OH}_{Cl} \longrightarrow (CH_3)_3N{<}^{OH}_{OCH_3} \quad (4)\ (5)$$

$$\text{II. } (CH_3)_3N{:}O \longrightarrow (CH_3)_3N{<}^{OCH_3}_{I} \longrightarrow (CH_3)_3N{<}^{OCH_3}_{OH} \quad (4)\ (5)$$

The trimethyl-hydroxy-ammonium methoxide formed in reaction I, quantitatively decomposes into methyl alcohol and trimethylamine oxide on evaporating the aqueous solution. The trimethyl-methoxy-ammonium hydroxide produced in reaction II, on the other hand, yields trimethylamine, formaldehyde and water. In addition to the above, several pairs of isomers of the type $(CH_3)_3N(OR')(OR'')$ were isolated. All of these could be decomposed to give trimethylamine, aldehyde and alcohol; in each case the alkyl residue occupying position (4) was liberated as aldehyde, and no trace of any other aldehyde could be detected. It follows, therefore, that the two alkoxy groups are not linked to nitrogen in the same manner. Meisenheimer assumed the five radicals to be attached to nitrogen by means of principal valencies, four in an inner and one in an outer zone (III and IV) as in Werner's theory.

$$\text{III. } \left[\begin{matrix} CH_3 \\ CH_3 \end{matrix} \cdot N \cdot \begin{matrix} CH_3 \\ OCH_3 \end{matrix}\right]OH \qquad \text{IV. } \left[\begin{matrix} CH_3 \\ CH_3 \end{matrix} \cdot N \cdot \begin{matrix} CH_3 \\ OH \end{matrix}\right]OCH_3$$

It was supposed that the group in the outer zone, at all events when the substance is in solution, resembled the labile group of a tautomeric compound in having no fixed position, and had therefore no apparent influence on the asymmetry of the molecule.

An explanation of the constitution of the amine oxides has been advanced by Lowry and Sidgwick (see p. 29) on the basis of the electronic theory.

(c) *Geometrical Isomerism of Nitrogen Compounds*

All nitrogen compounds capable of exhibiting geometrical isomerism are characterised structurally by a double bond between carbon and

[1] Meisenheimer, *Ber.*, 1908, **41**, 3966. *Ann.*, 1911, **385**, 117; 1913, **397**, 273; **399**, 371.

nitrogen, and the isomers bear the same relationship to one another as those of the ethylene series (p. 48).

Starting from the consideration that numerous compounds are known in whose molecule a N-atom plays the equivalent part of a CH-group (*cf.* benzene and pyridine, naphthalene and quinoline), Hantzsch and Werner suggested that the three valencies of the nitrogen atom are directed towards three summits of a tetrahedron, at whose fourth lies the nitrogen atom itself. Hence all compounds containing the divalent group *a*—C—*b* united to the divalent N—*c* should, by analogy with the ethylene derivatives, occur in two different configurations :

or representing the nitrogen compounds in perspective,

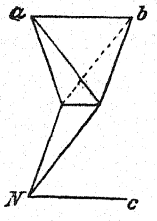


FIG. 12.

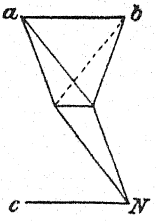
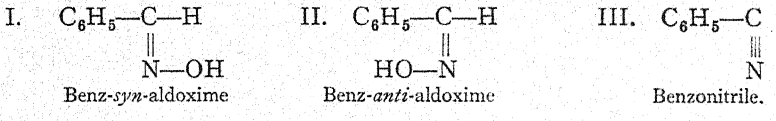
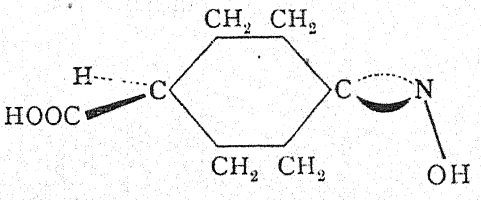


FIG. 13.

One of the most important and earliest investigated classes of this type is that of the oximes ; and in later years inquiry has been extended to the hydrazones, carbazones and imides.[1] The two isomeric benzaldoximes, for example, are given the configurations I and II following :



Strong confirmation of this theory is provided by the success of Mills and Bain in resolving the oxime of cyclohexanone carboxylic acid into optically active forms. The asymmetry of the compound can only be explained on the assumption that the hydroxyl of the oxime group lies in a different plane to that occupied by the H and COOH at the other end of the molecule.



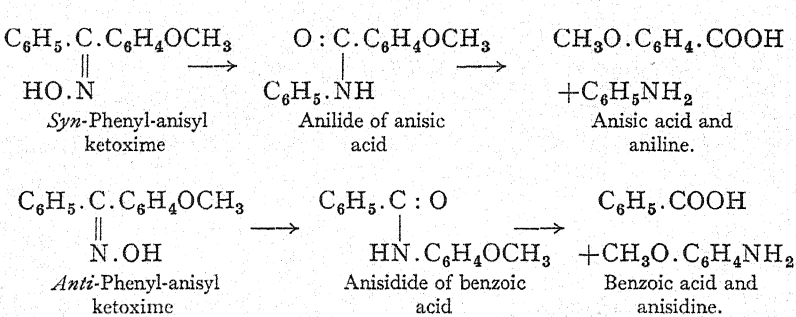
In agreement with the above theory, the symmetrical ketones, R_2CO, yield only one oxime, and the unsymmetrical ketones, R′R″CO, yield in

[1] Hantzsch, *Ber.*, 1897, **30**, 3003. Stieglitz, *Amer. Chem. J.*, 1908, **40**, 36. Busch, *Ber.*, 1912, **45**, 73.

general two, although in some cases only one is known, the other being apparently too unstable to be isolated. Similarly, a symmetrical diketone such as benzil, $C_6H_5.CO.CO.C_6H_5$, forms two monoximes and three dioximes.

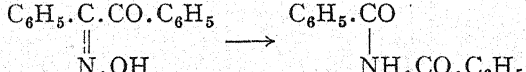
The *configurations of stereoisomeric aldoximes* were first deduced by methods devised by Hantzsch. One form readily loses water to yield a nitrile, whereas the other is more stable. It was therefore concluded that the former was probably a *syn*-aldoxime, with H and OH in close spatial proximity; and that the latter was an *anti*-aldoxime, with H and OH on opposite sides of the molecule. Still greater differences in ease of nitrile formation are shown by the acetyl derivatives of the oximes (p. 441).

Hantzsch deduced the *configurations of the ketoximes* by means of the Beckmann transformation (p. 182), which may be effected, for example, by treating the ketoxime in benzene solution with phosphorus pentachloride, when it is converted into a substituted amide. The two isomers yield different products, and Hantzsch assumed that the change occurred in the following manner, the hydroxyl group being supposed to exchange places with the adjacent radical in the *cis*-position, followed by a rearrangement to the substituted amide. As an example we may quote the case of the phenyl anisyl ketoximes.[1]



The constitution of the final product is then determined by hydrolysis to the acid and amine.

Using the same method, configurations were assigned to the two monoximes of benzil. The α-form, m.p. 140°, yields dibenzamide as sole product of the Beckmann transformation and was therefore given the following structure:



The β-form, m.p. 113°, was found to be converted through benzoyl

[1] In the aldoximes the prefix *syn-* indicates adjacent positions of the reactive groups H and OH. In the ketoximes the term *syn-* or *anti-* indicates the position relative to OH which is assumed by the group immediately following the prefix.

formanilide into phenyl isocyanide and benzoic acid. It was thus given the alternative formulation :

$$C_6H_5.C(=N.OH).CO.C_6H_5 \longrightarrow C_6H_5.NH.CO.CO.C_6H_5 \longrightarrow C_6H_5.COOH + C_6H_5.N{\equiv}C$$

In deriving stereochemical formulæ from an examination of intramolecular reactions such as these, it was at first assumed that the changes would proceed all the more readily the closer the reacting groups are to one another in space. Unfortunately, no facts were known by which the validity of this assumption could be strictly tested in the case of the oximes, and there has always remained the possibility that the Beckmann rearrangement, for example, does not involve an interchange of adjacent groups, but of groups in the *anti*-position. The whole question of the configuration of aldoximes and ketoximes has been reopened in recent years owing to the discovery of reactions which appear to reverse the accepted structures. Meisenheimer [1] found that when triphenyl iso-oxazole (I) is oxidised with ozone or chromic oxide, there is obtained a benzoylated benzil monoxime which on hydrolysis yields a benzil monoxime. We should expect this reaction to proceed according to the scheme

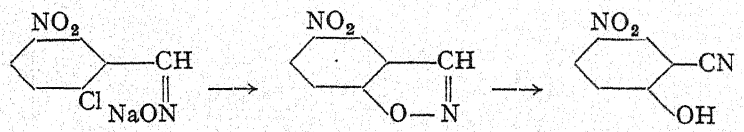
I. $$C_6H_5.C(=N.O.C.C_6H_5).C.C_6H_5 \longrightarrow C_6H_5.C(=N.O.CO.C_6H_5).CO.C_6H_5 \longrightarrow C_6H_5.C(=N.OH).CO.C_6H_5$$

The monoxime actually formed, however, melts at 113° and is the one which had previously been assigned the alternative structure.

Meisenheimer suggests that the oxidative disruption of triphenyl iso-oxazole may be brought into agreement with the results of the Beckmann change if it is assumed that in the latter an exchange occurs between the OH group and the radical in the *anti*-position.

$$R'.C(=N.OH).R \longrightarrow R'.C(=N).OH.R \longrightarrow R'.CO.NH.R$$

A similar reversal of Hantzsch's interpretation of the mechanism by which nitriles are formed appears to be indicated by the work of Bishop and Brady [2] on the conversion of aromatic aldoximes into iso-oxazole derivatives. One of the two 5-nitro-2-chloro-benzaldoximes

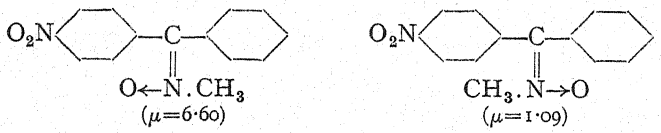


undergoes this change readily in the form of its sodium salt, the unstable benzo-isooxazole first produced being converted into the nitrile of 5-nitro-

[1] *Ber.*, 1921, 54, 3206; 1924, 57, 276. *Ann.*, 1925, 444, 94; 1926, 446, 205. [2] O. L. Brady and G. Bishop, *J. C. S.*, 1925, 127, 1357.

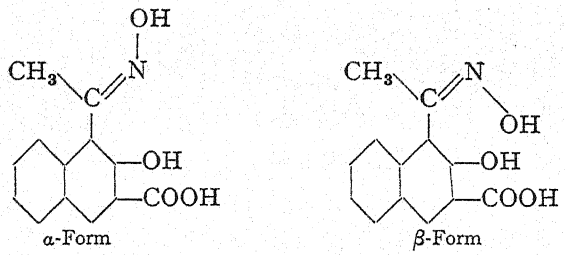
salicylic acid, and thus indicating the configuration given above. This isomeride, however, was originally assigned the reverse structure owing to the ease with which the acetyl derivative yields a nitrile.

Additional support for the modern point of view has subsequently been gained by the use of independent methods. A determination of the dipole moments (p. 80) of the N-methyl ethers of the two *p*-nitrobenzophenone oximes [1] shows that one has $\mu = 6{\cdot}60$ and the other $\mu = 1{\cdot}09$. Since the only strong dipoles present are those of the groups NO_2 and NO, it follows that in the former compound these dipoles must be in a position to reinforce one another, and that in the less polar form they are oriented in opposite directions. The configurations are therefore represented as follows, and are found to be in agreement with



the structures deduced from the Beckmann transformation of the oximes, using Meisenheimer's interpretation of the reaction.

Another interesting case is that of the oximes of 2-hydroxy-1-acetyl-3-naphthoic acid.[2] One of these, the *β*-form, was obtained in the optically

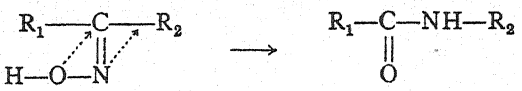


active state as its cinchonine and coniine salts, although on removal of the alkaloids racemisation rapidly ensued. The existence of an active form is explained by the "restricted rotation" (see p. 43) of the group attached to position 1 of the naphthalene nucleus, and the *β*-form is therefore given the structure indicated. No optical isomerism is exhibited by the *α*-form, in which it must be assumed that this group is free to rotate around the bond joining it to the aromatic radical. Beckmann transformations carried out with the *α*- and *β*-oximes are in agreement with these configurations, yielding compounds in which $\cdot NH \cdot CO \cdot CH_3$ and $\cdot CO \cdot NH \cdot CH_3$, respectively, are linked to position 1.

A suggestion which gives some insight into the mechanism of the Beckmann rearrangement has recently been advanced by Mills.[3] The driving force of the reaction is considered to be the superior affinity of

[1] L. E. Sutton and T. W. J. Taylor, *J. C. S.*, 1931, 2190. [2] Meisenheimer and co-workers, *Ann.*, 1932, **495**, 249. [3] W. H. Mills, *Presidential Address to British Association (Chemistry Section)*, 1932.

oxygen for the central carbon atom, which leads to the replacement of the weak O—N link by the stronger one joining oxygen to carbon. Under these conditions the first step in the reaction must be the movement of oxygen to carbon, thus displacing the nitrogen atom in a direction away from oxygen and in a sense corresponding to a *trans*-migration of the radicals attached to carbon.



(d) *Geometrical Isomerism in Compounds containing the Group* —N = N—

According to Hantzsch the diazo-compounds also exist in stereo-isomeric forms, the configurations of which are analogous to those of the ethylene derivatives. The experimental ground for this statement will be dealt with later (see p. 405) but the analogy in question may be illustrated by the following formulæ.

I. Ethylene Compounds

Cis-form *Trans*-form.

II. Carbon-Nitrogen Compounds

Syn-form *Anti*-form

III. Diazo-Compounds

Syn-form *Anti*-form.

The similarity of configuration can also be shown by use of the tetrahedron models, assuming as before that the valencies of trivalent nitrogen may under certain conditions be directed towards the three corners of a

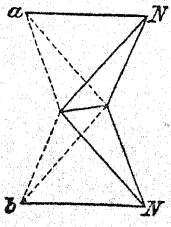


Fig. 14.

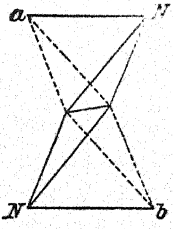
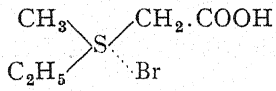


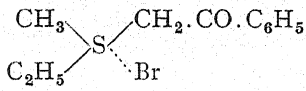
Fig. 15.

tetrahedron, at whose fourth lies the nitrogen atom itself. From this point of view the diazo-compounds appear as double tetrahedra with one edge in common, as in Figs. 14 and 15.

3. Stereochemistry of Sulphur Compounds

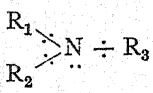
The success of Pope and Peachey in resolving a substituted ammonium salt gave a great impetus to the investigation of compounds containing asymmetric atoms other than carbon. *Optically active sulphur compounds* were obtained almost simultaneously by Pope and Peachey [1] and by Smiles.[2] The former resolved methyl ethyl thetine bromide (I) by bringing it into reaction with silver *d*-camphor-sulphonate and repeatedly recrystallising the resulting methyl ethyl thetine *d*-camphor-sulphonates from a mixture of alcohol and ether. The camphor-sulphonic group was then

I. 

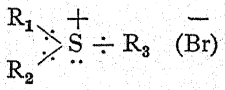
II. 

exchanged for platinic chloride, yielding an active double compound containing $PtCl_4$. Smiles resolved the methyl ethyl sulphide addition compound of ω-bromo-acetophenone II in a similar manner using *d*-camphor-sulphonic acid.

The optical activity of these compounds is not destroyed by the ionisation of bromine in aqueous or alcoholic solutions, and is therefore associated with the trisubstituted sulphonium ion. It is noteworthy that no activity has been found in the corresponding trivalent nitrogen



Inactive



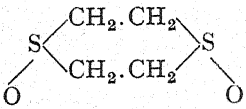
Active.

derivatives $NR_1R_2R_3$ despite the apparently identical arrangement of valency electrons around the two central atoms. Lowry has suggested that this is due to the greater mobility of atomic structure in the case of nitrogen, which leads to the immediate racemisation of the active forms.

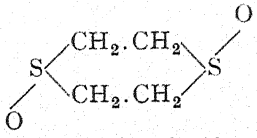
An interesting extension of our knowledge of the stereochemistry of sulphur was made some years later. It was found that sulphinic esters of the type, $CH_3.C_6H_4.SO.OC_2H_5$, may exist in the optically active state, a discovery which was followed up by the resolution of *m*-carboxyphenyl methyl sulphoxide $HOOC.C_6H_4.SO.CH_3$ and 4′-amino-4-methyl-diphenyl sulphoxide [3] $H_2N.C_6H_4.SO.C_6H_4.CH_3$. A carbon atom linked to oxygen by a double bond is regarded as having a plane of symmetry bisecting both atoms and the double bond, but no such symmetry can be present in the sulphoxide linking, since sulphoxides exist in mirror-image forms. Oxygen in these compounds is evidently disposed above or below the plane occupied by the group C—S—C, a conjecture which is supported by the isolation of dithian dioxide in

[1] *J. C. S.*, 1900, **77**, 1072. [2] *J. C. S.*, 1900, **77**, 1174. See also Pope and Neville.
[3] Phillips, *J. C. S.*, 1925, **127**, 2552; Harrison, Kenyon and Phillips, *J. C. S.*, **1926**, 2079.

(inactive) *geometrically isomeric forms*,[1] the oxygen atoms being arranged in the *cis*- or *trans*-positions with respect to each other.



Cis-dithian dioxide



Trans-dithian dioxide.

Asymmetry of Cobalt, Rhodium, Chromium and Iron Compounds. See Werner, *Ber.*, 1912, 45, 121 ; 1913, 46, 3674.

Optically Active Selenium Compounds. See Pope and Neville, *Proc. Chem. Soc.*, 1902, **18**, 198 ; **21**, 92.

Optically Active Tin Compounds. See Pope and Peachey, *Proc. Chem. Soc.*, **16**, 42, 116.

Optically Active Silicon Compounds. Kipping, *J. C. S.*, 1907, **91**, 209.

TAUTOMERISM, DESMOTROPISM, DYNAMIC ISOMERISM

There are a number of substances known which appear to exist in one form only, but give rise to two distinct series of derivatives. Familiar examples of this kind are hydrocyanic acid, which may react as hydrogen cyanide H—C≡N or as carbimide C=N—H, and cyanic acid, for which we have the possible formulæ O : C : NH and HO.C : N.

Such compounds, the constitution of which appears to vary with the reagent employed, are called tautomeric. The word **tautomerism**, therefore, in its original sense, denoted a special case of structural isomerism, in which only one form had been isolated.[2]

The earliest explanation of this phenomenon was based on the assumption that the mobile hydrogen atom was in a state of constant oscillation, and in consequence both parent forms could be imagined to be present in the one substance (Laar).[3] The non-existence of one of the expected forms was, however, first explained by postulating the occurrence of a labile modification, having a pronounced tendency to undergo intramolecular rearrangement into the stable isomeride.

In the year 1880 Erlenmeyer stated that all secondary alcohols, in which the two affinities of the group =CH.OH are united to another carbon atom by a double bond, are at the moment of their formation transformed into aldehydes ; and in the same way tertiary alcohols of

[1] E. V. Bell and G. M. Bennett, *J. C. S.*, **1927**, 1798. For other compounds of similar type see E. V. Bell and G. M. Bennett, *J. C. S.*, **1928**, 86 ; **1929**, 15. F. G. Mann and Sir W. J. Pope, *J. C. S.*, **1922**, 1052. [2] Our knowledge of dynamic isomerism has been greatly extended in recent years through the work of Thorpe and Ingold. These authors adopt *tautomerism* as a general term to cover all examples of chemical change involving the existence of isomers in a state of equilibrium, even though special conditions may be required to bring about this state (see p. 64 *et seq.*). [3] The word tautomerism was first employed by Laar, in connection with his theory of oscillations.

this type (with the exception of the phenols) isomerise into ketones. Those chemical reactions, for example, which might be expected to yield vinyl alcohol, $CH_2{=}CH{-}OH$, invariably lead to the formation of the isomeric aldehyde, $CH_3{-}CH{=}O$.

Similar conclusions were arrived at by Baeyer in 1883, from his work on the derivatives of isatin. He found that the isomerism exhibited by these derivatives (see p. 634) disappeared when the parent substance was regenerated in the free state. Isatin itself could be isolated in one form only, and the instability of the other theoretically possible isomeride was ascribed to the mobility of an atom of hydrogen, the replacement of which by another group rendered this configuration also stable. Baeyer called the labile modification the " pseudo-form."

The oscillation theory of tautomerism was first proposed by Kekulé, in connection with the constitution of benzene (p. 359), and later taken up by Laar : it assumes the hydrogen atom to alternate rapidly between two extreme positions of equilibrium, the alternation producing a corresponding change of single to double linking, and *vice versa*, between two adjacent carbon atoms.

The work of later investigators,[1] however, has shown the explanation advanced by Baeyer to be the correct one. Tautomerism is due to the existence of two labile forms in equilibrium with each other, the isomerism in the majority of cases being caused by the transfer of a hydrogen atom from one carbon atom to another which is in close proximity to the first, accompanied by the necessary rearrangement of single and double bonds. Nitrogen may also function in the same manner as carbon in this interchange (see p. 65).

Knorr has advanced a general theory of tautomerism which is outlined in the following paragraphs. Structural isomers which differ only in the position of a hydrogen atom within the molecule are termed *desmotropes*, and in actual practice the isolation of both isomerides of this type has only been attained in a few cases. Tribenzoyl methane, for example, has been prepared in the two forms

Keto-form Enol-form.[2]

In the vast majority of cases the isomerides are only realisable in the form of derivatives, one parent substance alone being known. Such a substance, as already stated, is then called *tautomeric*.

Tautomerism therefore depends primarily on one compound reacting in two different forms, and thus giving rise to two series of derivatives.

[1] Wislicenus, *Ann.*, 1896, **291**, 147. Hantzsch, *Ber.*, 1896, **29**, 699, 2251 ; 1898, **31**, 2854 ; 1899, **32**, 575, 1723, 3066 ; 1906, **39**, 1084. Knorr, *Ann.*, 1899, **306**, 332. Lowry, *J. C. S.*, 1899, **75**, 211. Rabe, *Ann.*, 1900, **313**, 129. K. H. Meyer, *Ann.*, 1913, **398**, 63. [2] The term " enol " is derived from " en," indicating the double bond, and " ol," representing the alcoholic hydroxyl group.

This common property of all tautomeric compounds serves as a general definition of the term tautomerism.

Further sub-classification of these substances is most conveniently based on the degree of mobility of the hydrogen atom.

In cases where both the isomerides predicted by theory have been isolated these are frequently termed *dynamic isomers* (Lowry) or *desmotropic compounds*, to distinguish them from the single tautomeric substance. Dynamic isomers are characterised by a tendency to undergo isomerisation into the other form. In general, therefore, they are not stable in solution or in the fluid state. Solution or fusion of either form usually results in the production of a mixture containing the two isomerides in a state of equilibrium. Such a mixture is described by Knorr as an "*allelotropic mixture*." The rates of isomerisation of the two forms may assume all possible values, the same naturally holding true for the ratio of the two isomers in equilibrium, since this itself depends on the relative rates of change.

It frequently happens that the amount of one of the forms in the equilibrium-mixture becomes so small as to be negligible. In such cases this labile form, no longer traceable by analytical methods, corresponds to the pseudoform of Baeyer.

On the other hand, if we imagine the forms in an allelotropic mixture to isomerise with equal and very great velocities, we have a picture of a limiting case conforming to Laar's oscillation hypothesis.

Fluid tautomeric substances, such as hydrocyanic acid (p. 328), would appear to fall under the heading of allelotropic mixtures, except in the limiting cases discussed above.

A solid tautomeric substance can, in most instances, be assigned a definite structure. This, however, cannot be determined with certainty by chemical means, and recourse is usually had to methods involving a comparison of the substance with its derivatives or with other desmotropic isomerides of known constitution. Physical methods are of the greatest value in this connection.

For other examples of tautomerism see pp. 65-71, also isatin, p. 634, acetoacetic ester, p. 266, and pyrazole derivatives, p. 655.

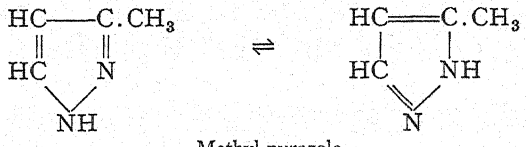
A more general view of dynamic isomerism has been adopted in the extensive researches carried out in recent years by Thorpe and Ingold. All examples of dynamic isomerism are classed by these authors under the heading of tautomerism, including cases in which both forms are readily isolated or in which the attainment of equilibrium requires special temperature conditions or the addition of a catalyst. Thorpe and Ingold [1] have revived and extended an earlier classification of Laar [2] by which tautomeric compounds are grouped according to the type of mobile system present, e.g. *dyads*, containing two polyvalent elements linked

[1] Quelque nouveaux Aspects de la Tautomerie, *Bull. Soc. Chim.*, 1923. [2] *Ber.*, 1885, 18, 648.

together, the labile hydrogen atom travelling from one to another of these : *triads* in which the original polyvalent elements are separated by a third, the H-atom now travelling from the first to the third atom in the chain, and so on.

Dyads.—A simple representative of this class is hydrogen cyanide, which is probably a tautomeric mixture of the structures H—C≡N and H—N⩲C (see p. 328). Although only one form of the acid is known it yields two series of alkyl derivatives of the types R.CN and R.NC.

Another example is methyl pyrazole (p. 655), which gives rise to two N-phenyl derivatives and may therefore be written as



Methyl pyrazole

Triads.—Triad systems include a large number of types, chief among which are the following :—

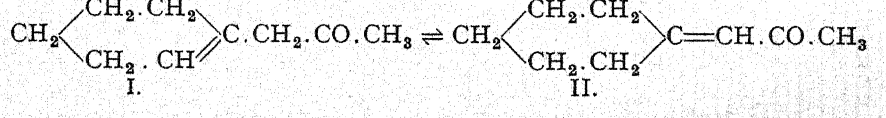
(1)	Three-carbon system	C—C—C
(2)	Diazo-amino system	N—N—N
(3)	Cyanide-imide system . . .	C—C—N
(4)	Keto-enol system	C—C—O
(5)	Amidine system	N—C—N
(6)	Amido-imidol system . . .	N—C—O
(7)	Hydrazone-azo system . . .	C—N—N
(8)	Nitro-pseudonitro system . . .	C—N—O

Only the more important of these can be mentioned here. In the following paragraphs the use of an arrow indicates the alternative position to which the hydrogen atom may travel.

(1) *The Three-carbon System*, $\overleftarrow{C{=}C{-}CH}$. The possibility of tautomerism of this kind is indicated by the transformation of $\beta\gamma$-pentenic acid into the $\alpha\beta$-acid on being boiled with alkali (Fittig [1]). In this case both forms are usually stable and readily isolated. A more mobile iso-

$$CH_3.\overleftarrow{CH}:CH.CH_2.COOH \longrightarrow CH_3.CH_2.CH:CH.COOH$$

merism has, however, been shown to occur in the following ketonic compounds by Birch, Kon and Norris.[2]

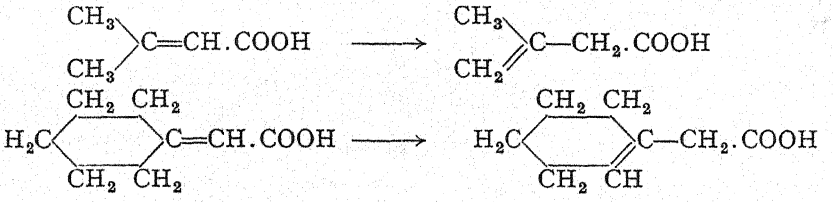


I. II.

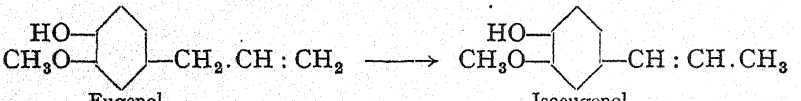
These form an equilibrium mixture containing a very large proportion of I.

[1] *Ber.*, 1891, **24**, 82 ; 1894, **27**, 2677 ; *Ann.*, 1896, **299**, 1. [2] *J. C. S.*, 1923, **123**, 1361.

Among the acids investigated by Fittig the direction of the shift was from the $\beta\gamma$- to the $\alpha\beta$-position. Kon and his co-workers, who have examined a large number of cases of this nature, have shown that the mobility of the hydrogen atom and the relative stability of the two forms depends on the nature of the other groups present in the molecule. For example, in the *gem*-dialkyl acrylic acids and cyclo-hexylidene-acetic acids, the $\beta\gamma$-unsaturated derivatives are the more stable.



A similar isomeric change occurs in the transformation of eugenol into isoeugenol under the influence of hot alkalis, and in many terpene derivatives.



Eugenol — Isoeugenol.

Glutaconic Acids.—Under the heading of triads are included glutaconic acid, $HOOC.CH_2.CH:CH.COOH$, and its derivatives which have been extensively investigated by Thorpe and his co-workers.[1] Compounds of this type which contain mobile hydrogen furnish interesting examples of three carbon tautomerism accompanied by geometrical isomerism. In the case of the unsubstituted acid, the migration of a hydrogen atom leaves the molecular structure unchanged, although as has been pointed out by Packer and Thorpe,[2] the movement may or may not be accompanied by some interconversion of the *cis*- and *trans*-configurations, depending upon the spatial arrangement of the CH_2COOH group at the moment of transfer.

The arrangement of the constituent atoms in space is assumed to be governed by the tendency for similar groups to take up positions as remote as possible from one another. Such a tendency in the above acids can be satisfied owing to the power of free rotation about the single bond. It would thus be expected that the tautomeric change in the case of *trans*-glutaconic acid would take place mainly without alteration in the stereochemical configuration but that the *cis*-acid would be largely converted into the *trans*-form.

In compounds such as $\alpha\alpha$-dimethyl glutaconic acid (I) and $\alpha\alpha\beta$-trimethyl glutaconic acid (II), the last mobile hydrogen atom has been

[1] *J. C. S.*, 1905, **87**, 1669; Thorpe and Thole, *J. C. S.*, 1911, **99**, 2187; Goss, Ingold and Thorpe, *J. C. S.*, 1923, **123**, 327. [2] J. Packer and J. F. Thorpe, *J. C. S.*, **1926**, 1199.

replaced by an alkyl group. These acids only exist in the usual *cis*- and *trans*-isomerides, of which the former alone yield anhydrides. Ordinary glutaconic acid, although of the *trans* type, also yields an anhydride. The latter, however, presumably corresponds to the *cis*-acid, as on treatment with cold water it is converted into the very unstable *cis*-glutaconic acid.[1] Anhydride formation is here due to the mobility of the glutaconic structure and is apparently preceded by isomerisation into the *cis*-acid.

Tautomerism plays a more definite part in the case of alkyl substituted acids containing mobile hydrogen. Although many of these also exist in two modifications, the isomerism is not that of the ordinary geometrical type. Thorpe and Thole therefore suggested that the compounds are mobile tautomeric substances in which the α- and γ-carbon atoms function equally. Support for this view is given by the work of Feist,[2] who found that the ozonides of unsymmetrically substituted esters of glutaconic acid decomposed to give *four* products, two corresponding to each of the two possible positions of the double bond, instead of yielding the *two* products to be expected from a static compound with the double bond in a fixed position. The changes may be illustrated by the case of β-phenyl-α-methyl-glutaconic ester which on ozonisation gave a mixture of the esters of benzoyl-acetic, pyruvic, glyoxylic and α-benzoyl-propionic acids.

$$\begin{array}{l} \mathrm{EtOOC.CH_2.C(C_6H_5):C(CH_3).COOEt} \rightarrow \mathrm{C_6H_5.CO.CH_2.COOEt} + \mathrm{CH_3.CO.COOEt} \\ \qquad\qquad\qquad\qquad\quad \uparrow\downarrow \\ \mathrm{EtOOC.CH:C(C_6H_5).CH(CH_3).COOEt} \rightarrow \mathrm{O:CH.COOEt} + \mathrm{C_6H_5.CO.CH(CH_3).COOEt} \end{array}$$

Hence there is a symmetry about the molecule of glutaconic acid which is not conveyed in the usual formula with a fixed double bond. The earlier suggestion that the stable acids were represented by symmetrical formulæ, such as III ("normal" form), has now been

III. $\mathrm{HC}\begin{cases} \mathrm{CH.COOH} \\ [\mathrm{H}] \\ \mathrm{CH.COOH} \end{cases}$ IV. $\mathrm{HC}\begin{cases} \mathrm{C(CH_3).COOH} \\ \mathrm{CH(CH_3).COOH} \end{cases}$

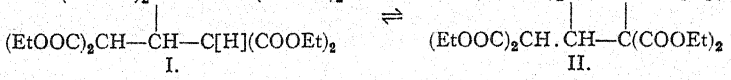
negatived by the resolution of $\alpha\gamma$-dimethyl glutaconic acid (IV) into optically active components.[3] Such a resolution could not have been effected had the molecular structure been of the symmetrical "normal" type, although it is possible that the latter form may exist as an ephemeral intermediate phase.

Ring-chain Tautomerism.—Thorpe and Ingold conclude that in every triad system tautomerism may occur between open-chain and cyclic forms, *e.g.*

$$\mathrm{A}\begin{cases} \mathrm{Y{=}Z} \\ \mathrm{X(H)} \end{cases} \rightleftharpoons \mathrm{A}\begin{cases} \mathrm{Y{-}Z(H)} \\ \mathrm{X} \end{cases}$$

[1] Malachowski, *Ber.*, 1929, **62**, 1323. [2] Feist, *Ann.*, 1922, **428**, 25-75. [3] T. H. McCombs, J. Packer and J. F. Thorpe, *J. C. S.*, 1931, 547.

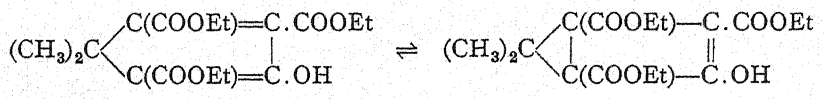
As an example of this type of change we may mention the esters I and II (prepared from ethyl α-carboxy-glutaconate, $(EtOOC)_2CH.CH:CH.COOEt$, by treatment with piperidine).[1] Both isomerides have



I. II.

been isolated in the pure state, and the equilibrium is readily followed in solution.

Intra-annular tautomerism occurs when an equilibrium exists between two cyclic isomerides with or without the migration of an atom of hydrogen. An example of the latter type is furnished by the cyclopentadiene derivatives [2] of the following structure:



(2) *Keto-enol System*, C=C—OH. This includes acetoacetic ester (which is fully discussed on p. 266 *et seq.*) and many of the well-known examples of tautomerism, the equilibrium here occurring between the forms CH—C=O and C=C—OH.

$$\underset{\text{Keto form}}{CH_3.CO.CH_2.COOEt} \rightleftharpoons \underset{\text{Enol form.}}{CH_3.C(OH):CH.COOEt}$$

In addition to other β-ketonic esters, this group includes various 1 : 3-diketones, such as acetyl-acetone, $CH_3.CO.CH_2.CO.CH_3$; malonic ester; cyanacetic ester; and many cyclic derivatives which exhibit the properties of both ketones and hydroxy compounds, *e.g.* phloroglucinol (p. 430), resorcinol (p. 428) and camphor (p. 485).

(3) *Diazoamino System*, N=N—NH. When diazobenzene chloride is allowed to react with *p*-toluidine the product is identical with that obtained from the interaction of *p*-diazotoluene and aniline, although on the ordinary formulation two different products would have been expected.[3]

$$C_6H_5.N:N.Cl+H_2N.C_6H_4.CH_3 = C_6H_5N:N.NH.C_6H_4.CH_3 \quad (a)$$
$$CH_3.C_6H_4.N\ N.Cl+H_2N.C_6H_5 = CH_3.C_6H_4.N:N.NH.C_6H_5 \quad (b)$$ } A

The two end-products are therefore represented as tautomeric forms in equilibrium with one another. This view is supported by the fact that when the double bond is disrupted by reduction or hydrolysis, *four* products are obtained, two corresponding to each of the theoretically possible forms.[4] (Compare three-carbon system, p. 65.) For example,

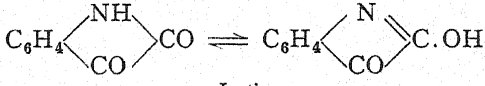
[1] Ingold, Perren and Thorpe, *J. C. S.*, 1922, 1765. [2] W. H. Perkin and J. F. Thorpe, *J. C. S.*, 1901, 79, 729. See also *Ann. Rep. Chem. Soc.*, 1927, 117. [3] Meldola and Streatfield, *J. C. S.*, 1887, 51, 102, 434. [4] Noelting and Binder, *Ber.*, 1887, 20, 3004.

the above product A gives on reduction a mixture of aniline, and *p*-tolylhydrazine (from *a*) together with *p*-toluidine and phenylhydrazine (from *b*).

(4) *Cyanide-Imide System*, $\overleftarrow{C{=}C{=}NH}$. Few examples of this group are known, one of the best investigated being cyanocamphor [1]

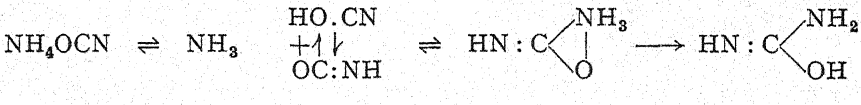
which has been isolated in two interconvertible forms.

(5) The *Amido-Imidol System*, $\overleftarrow{N{=}C{-}OH}$, involves an equilibrium between the two structures $\begin{matrix} N{=}C{-}OH \\ | \quad | \end{matrix}$ and $\begin{matrix} HN{-}C{=}O \\ | \quad | \end{matrix}$. Compounds of this kind have long been known in isatin, indoxyl and oxindole (see Index).



Isatin

Another example is cyanic acid, which according to E. A. Werner [2] represents an equilibrium mixture of the same type, the conversion of ammonium cyanate into urea being formulated as follows :—



Werner also regards urea as exhibiting similar tautomerism

(6) *Amidine System*, $\overleftarrow{N{=}C{=}NH}$. A simple example of this triad system is cyanamide,[3] which is probably an equilibrium mixture of the type $N{:}C.NH_2 \rightleftharpoons NH:C:NH$. The unsymmetrical formula is supported by the formation of cyanamide from cyanogen chloride and ammonia, $CN.Cl + NH_3 \longrightarrow CN.NH_2 + HCl$. Cyanamide yields two isomeric series of alkyl derivatives, pointing to an alternative structure. Diethylcyanamide on hydrolysis with acids decomposes into diethylamine, ammonia and carbon dioxide. It is therefore formulated as $N{:}C.NEt_2$.

$$N{:}C.NEt_2 + 2H_2O = NH_3 + CO_2 + HNEt_2$$

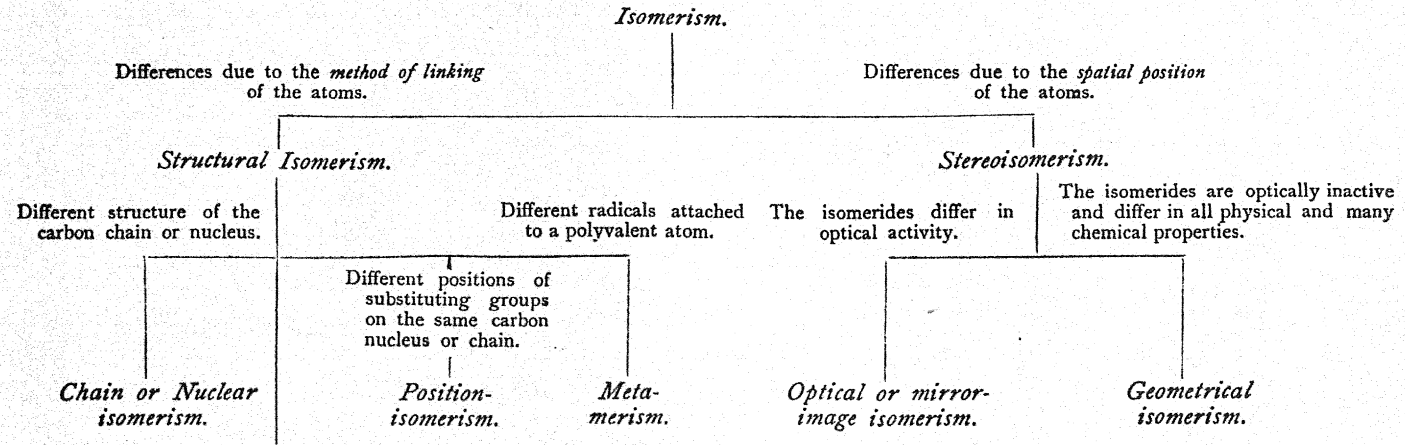
[1] Hantzsch and Osswald, *Ber.*, 1889, **32**, 641. [2] *J. C. S.*, 1913, **103**, 1010, 2275; 1914, **105**, 923; 1915, **107**, 715; 1918, **113**, 694; 1919, **115**, 1093. [3] E. A. Werner, *J. C. S.*, 1915, **107**, 715.

Polymerism.

Compounds have the same percentage composition (*i.e.*, same empirical formula), but have different molecular weights and different properties.

Isomerism.

Compounds have the same percentage composition and same molecular weight (*i.e.*, same molecular formula), but have different properties.



The isomerides differ only by the position of a hydrogen atom in the molecule, and are characterised by a tendency to undergo mutual isomerisation :

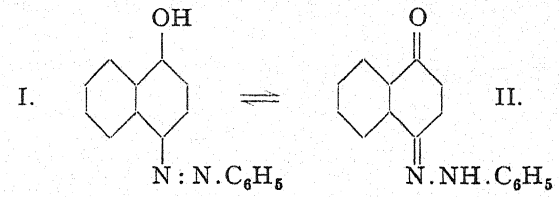
Tautomerism or *Dynamic isomerism.*

The diphenyl derivative, diphenyl carbodiimide, on the other hand, yields under the same treatment aniline and carbon dioxide, and is assigned the symmetrical structure.

$$C_6H_5.N:C:N.C_6H_5 + 2H_2O = 2C_6H_5.NH_2 + CO_2$$

Tautomerism of this kind was early discovered among the amidines by von Pechmann.[1]

(7) *Azo-Hydrazone System*, $\overleftarrow{\text{C=N—NH}}$. Laar [2] pointed out that the product (I) obtained by the interaction of diazobenzene chloride and naphthol is identical with (II) prepared from phenylhydrazine and α-naphthoquinone.



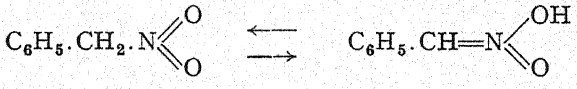
Probably there is actually an equilibrium between the two possible forms, one of which is so unstable as to disappear in the final product.

Similarly, R. Meyer found that when diazobenzene chloride is combined with sodio-malonic ester and the product hydrolysed, the substance obtained is identical with that prepared from phenylhydrazine and mesoxalic acid. It may therefore be represented either as a hydrazone IV,

$$C_6H_5.N_2.Cl + NaCH(COOEt)_2 \longrightarrow C_6H_5.N:N.CH(COOH)_2 \text{ III.}$$
$$C_6H_5.NH.NH_2 + O:C(COOH)_2 \longrightarrow C_6H_5.NH.N:C(COOH)_2 \text{ IV.}$$

or as an azo-compound III.

(8) *Nitro-Pseudonitro System*, $\overleftarrow{\text{C=N—OH}}$ (with ‖ O). This type of isomerism is exhibited by primary and secondary nitro compounds and is fully discussed on p. 165.



PHYSICAL PROPERTIES OF ORGANIC COMPOUNDS [3]

In respect of physical properties there is no general difference to be traced between carbon compounds and those of other elements.

In modern times the investigation of physical properties has become of great importance in the study of organic compounds, being of value

[1] *Ber.*, 1895, **28**, 869, 2392; 1897, **30**, 1779, 1783. [2] *Ber.*, 1885, **18**, 648. [3] Compare Smiles, *Relations between Chemical Constitution and Physical Properties* (Longmans).

not only for the purpose of identification but also as a means of attacking the problem of molecular constitution.

1. Colour [1]

Among those properties which make their appeal directly to the senses that of colour stands out prominently. Some organic compounds possess colour and others are colourless. A careful distinction, however, must be drawn between colour and the ability to function as a dye. A compound may be strongly coloured and yet have no power, even with the aid of a mordant, to fix itself on the fibres of cotton, wool or silk.

Despite much experimental investigation from various quarters, the problem of the relation between colour and constitution is still unsolved. One of the main difficulties lies in the complexity of all the contributory factors. So far, no clear insight has even been obtained into the purely physical processes on which the phenomenon of colour depends, although it is known that the appearance of colour in a compound is connected with its power of absorbing rays of certain wavelengths. For a proper understanding of the relationship between colour and constitution we also require to know more about the inner structure and state of vibration of the molecule. At present all that can be said is that a number of regularities have been discovered bearing upon this point.

It appears from numerous researches, carried out for the most part within the last thirty years, that double bonds of practically any kind are the primary cause of colour. Apart from their mere presence, the position they occupy within the molecule also plays an important rôle. Following a suggestion of Witt,[2] the term **chromophore** has been applied to all those groups which give rise to colour when allied in suitable manner and sufficient number with hydrocarbon radicals. In general, however, the full development of colour is not attained in combination with hydrocarbon radicals alone, but only when the influence of the chromophore is strengthened by the presence of certain other groups, which Witt calls **auxochromes**. The most important chromophores are the groups :

C=C,	C=O,	C=N,	N=N,	N_2O,	N=O
	Carbonyl,		Azo-,	Azoxy-,	Nitroso-group.

Among coloured hydrocarbons may be mentioned fulvene,[3] which contains three of the groups C=C. The presence of one or even of two such groups does not result in the production of any colour. Another comparatively weak chromophore is the carbonyl group. Colour is first noticeable in the presence of two of these, and then only if they are in very close proximity to one another. Thus diacetyl, $CH_3.CO.CO.CH_3$, with two carbonyl groups adjacent to one another, is a yellow liquid. The azo-group, on the other hand, is one of the strongest chromophores, even so simple a compound as diazomethane, CH_2N_2, being yellow; whilst azobenzene, $C_6H_5—N=N—C_6H_5$, forms orange-red crystals. Another strong chromophore is the nitroso-group, the true nitroso-compounds being coloured an intense blue or green in the liquid state or in solution.

[1] See also Kauffmann, *Ueber den Zusammenhang zwischen Farbe und Constitution bei chemischen Verbindungen* (Ahrens Sammlung, vol. ix., 1904. Also vol. xii.). [2] Witt, *Ber.*, 1876, 9, 522. [3] Thiele, *Ber.*, 1900, 33, 666.

The physicist Hartley found that benzene and many of its colourless derivatives show an absorption spectrum with the short ultra-violet rays, and are therefore coloured in the wider sense of the term. In his opinion each benzene derivative may be converted into a coloured substance by chemical changes, which result in the displacement of one or more absorption bands into the visible part of the spectrum. This is achieved by introducing atomic complexes into the benzene ring which damp its natural period of vibration.

The term chromophore has thus gradually acquired a new meaning as a result of recent research. The production of colour is believed to be due, not so much to the presence of certain combinations of atoms, as to the secondary influence they exert on the molecule in displacing its period of oscillation into the visible part of the spectrum. Coloured compounds have also been discovered possessing none of the so-called chromophore groups. In general, coloured compounds are those in which the atomic arrangement so modifies the vibration of the molecule as to produce an absorption band in the visible part of the spectrum.

The auxochromes, the most important of which are the amino-group (NH_2) and the hydroxyl group (OH), may act in two ways. On the one hand they may, by their presence, endow a substance with the capacity for salt-formation, with the possible production of a dye-stuff; and on the other, their introduction may lead to a deepening and intensification of the original colour. Those compounds containing a chromophore group, in which the entrance of an auxochrome produces a more strongly coloured substance or dye-stuff, are termed *chromogenes* by Witt.

In many cases the sharp distinction implied in the separation of groups into chromophores and auxochromes is scarcely justified, since the latter may be able to function as the former in calling forth the characteristic colour.[1]

It will be noticed over and over again in connection with the discussion of coloured substances and dye-stuffs, that there is a strong tendency to associate colour with the presence of double bonds and in particular of a quinonoid structure in the molecule.

The suggestion frequently advanced, that colourless substances may develop colour by simply passing into the ionic state, has been definitely disproved by Hantzsch. The colour of a compound is independent of the presence or absence of ions.

Phototropy[2] is the property possessed by some substances of changing colour according to the intensity and wave-length of the incident light. It has been thoroughly investigated in the case of the fulgides by Stobbe.

That the colour of solid matter varies continuously with the temperature has frequently been observed with organic compounds. The backward and forward continuity of the colour alteration is a special characteristic of this kind of reversible change. Stobbe, by whom this

[1] Hantzsch, *Ber.*, 1906, **39**, 1091. [2] Stobbe, *Ann.*, 1908, **359**, 1. *Ber.*, 1913, **46**, 1226.

phenomenon has also been examined in the case of the fulgides,[1] has described such compounds as *thermochromatic*.

2. State of Aggregation of Organic Compounds, Crystallisation

Comparatively few organic compounds are gaseous at the ordinary temperature, the majority of them exist normally in the liquid or solid state. In the latter case they may be amorphous or crystalline. Of these, the amorphous substances approximate more closely to liquids in their molecular condition, and their manipulation in the laboratory offers much greater difficulty than that of crystalline compounds. The crystalline form of an organic compound is often an important criterion of its identity.

To purify a substance by crystallisation, it is usually dissolved by heating with a suitable solvent, filtered from any undissolved impurities and the warm solution allowed to cool. The greater part of the dissolved material then separates in the crystalline state, while the small impurities remain dissolved in the mother-liquor. Crystallisation is also employed for separating the individual constituents of a mixture from one another (*fractional crystallisation*). In some cases the organic substance may separate in the form of an addition compound with the solvent.

Many carbon compounds have the property of crystallising in two or more distinct forms, a phenomenon known as *dimorphism* or *polymorphism*. Hexachloroethane, for example, may separate in crystals belonging to the rhombic, triclinic or cubic system.

Comparatively little is yet known as to the relation between chemical constitution and the crystal form of organic compounds. It has been established, however, that a definite connection exists between symmetry and asymmetry in molecule and crystal, and that changes in the chemical structure of the molecule also affect the conformation of the crystal. Asymmetry has already been discussed in dealing with the stereoisomerism of asymmetric carbon compounds (p. 32). The two stereoisomerides may differ in their configurations in such a way that they appear as enantiomorphous mirror-images of one another. Corresponding to this we often find a similar enantiomorphous difference in their crystal forms.

3. Melting-point

Under the influence of heat, solid compounds generally change their state of aggregation and become fluid. In many cases, however, chemical change takes place, followed by decomposition and the formation of new compounds. Those substances that are fusible without decomposition possess a definite melting-point. At this point the solid and liquid forms of a body are in equilibrium with one another; the melting-point therefore coincides with the freezing-point.

The melting-point is one of the most important physical constants

[1] Stobbe, *Ann.*, 1911, **380**, 17.

of an organic compound. In the vast majority of cases it is used for the identification of a substance and gives, in addition, valuable information as to the state of purity. While small impurities often bring about a considerable depression of the melting-point, larger amounts cause irregular and protracted melting, so that it is no longer possible to determine the point with certainty. Phenanthraquinone, for example, melts at 206°, 2-chloro-phenanthraquinone at 236°, but a mixture of the two in equal portions melts indefinitely between 160° and 190°.

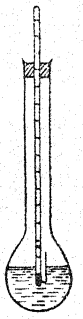


FIG. 16.

The melting-point is usually determined in an apparatus such as that illustrated in Fig. 16 or by use of a beaker provided with a glass stirrer. A few milligrams of the dry, finely powdered substance are contained in a capillary tube, closed at its lower end and made to adhere to the stem of a thermometer which is immersed in castor oil or strong sulphuric acid. Unless the melting-point is quoted as "uncorrected," a correction should be made for the portion of the mercury thread of the thermometer which is not immersed in the liquid.

Electrically heated apparatus is now in use in which a minute quantity of material is observed on the stage of a microscope. This is especially convenient for compounds melting above 200°, or which are only available in small amount.

The melting-point of successive members of a homologous series rises gradually with increase of molecular weight, but this is often accompanied by a minor alternation of rise and fall throughout the series. Members with an uneven number of carbon atoms have frequently a lower melting-point than the preceding compound containing one carbon atom less.

Among structurally isomeric compounds, that which is most symmetrically built usually has the highest melting-point. Thus of the isomeric di-substituted derivatives of benzene, the para-compound melts higher than the ortho- or meta-compounds.

A knowledge of the *melting-points of mixtures* is of special interest to the practical worker. At a certain composition the melting-point of a mixture of two substances reaches a minimum which lies below the melting-point of either of the two constituents. Two substances are therefore identical when a mixture of the two in any proportions has the same melting-point as either of the pure substances. The melting-point and composition of a mixture of substances is changed by repeated recrystallisation, and hence the constancy of the melting-point under this treatment is strong proof of the homogeneity and purity of the starting material.

4. Boiling-point and Distillation

The boiling-point of a liquid possesses the same importance as the melting-point of a solid, and is of great utility in the recognition, separation and purification of those compounds which are volatile without decomposition.

In most cases the boiling-point is determined by the same process of distillation which serves for its purification and isolation. A distillation flask (see Fig. 17) is about two-thirds filled with the liquid, and closed by a cork bearing a thermometer, the bulb of which should be a little below the side tube of the flask. In dealing with easily volatile substances the side tube is usually connected to a condenser. When the liquid is heated to boiling-point, the vapours escaping through the side tube heat the thermometer bulb on their way and are again cooled to the liquid form in the condenser. The contents of the flask are boiled vigorously, and if the liquid is homogeneous the thermometer remains steady throughout the whole period of distillation at a temperature representing the boiling-point. If desired, a correction may be made for that part of the thermometer thread not heated by the vapour, and should the barometric pressure be other than 760 mm. it should be noted, or a correction applied.

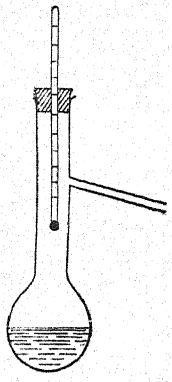


FIG. 17.

Many substances which cannot be distilled under ordinary barometric pressure owing to decomposition may be safely distilled under diminished pressure. In this case the internal pressure must be quoted with the boiling-point. Distillation under diminished pressure is a most valuable means for the isolation and purification of high-boiling compounds, and plays an important rôle in laboratory as well as in technical work.

A further form of distillation, frequently employed in the separation and purification of compounds sparingly soluble in water, is *distillation in steam*. Many such compounds, even those of high boiling-point or which cannot be distilled alone without decomposition, volatilise more or less easily when heated with water, or when steam is blown through the mixture. The boiling-point of a mixture of two liquids, which do not dissolve one another, is attained when the sum of their respective vapour pressures is equal to the external (atmospheric) pressure. When this is the case both liquids distil. Since water is generally by far the more volatile of the two, it follows that the other liquid distils at a temperature much below its normal boiling-point. Steam distillation, therefore, is merely a special case of distillation under diminished pressure.

In order to isolate the individual constituents from a mixture of volatile compounds we make use of *fractional distillation*. This serves as a means of separation when there is a sufficient difference between the respective boiling-points of the constituents. Only if the boiling-points of two liquids lie far apart is it possible to attain a comparatively complete separation in one distillation. In this case the lower boiling compound comes over first at an approximately constant temperature, which then rises rapidly to the boiling-point of the less volatile compound, this finally distilling over pure. Generally speaking, however, it is not possible to obtain even an approximate separation in this way by a single

distillation, and the process must be repeated several times. The efficiency of the operation is greatly increased by making use of a device known as a fractionating head (as designed by Wurtz, Hempel, Young and others) which brings about a partial condensation of the escaping vapour, returning the liquid so formed to the distillation vessel. In technical work a similar principle is adopted in "fractionating columns" (and dephlegmators), such as are described later under the purification of alcohols and benzene hydrocarbons.

Kopp was the first to point out the relationship existing between the constitution and boiling-point of an organic compound, and although the laws derived by him have not proved generally applicable, they nevertheless gave rise to a number of other fruitful investigations on the subject.

In a *homologous series* the boiling-point usually rises from member to member with increase in molecular weight. In the case of the normal primary alcohols, for example, the boiling-point rises at first fairly regularly by 18° to 22° for each additional CH_2 in the molecule. This increase gradually diminishes as we pass up the series. With the mixed aromatic hydrocarbons, the entrance of a CH_3 group into the side chain produces the same difference in boiling-point as with the homologues of the fatty series, *i.e.* about 18° to 22°; the entrance of a CH_3 group into the benzene ring, however, raises the boiling-point about 30°.

Regularities may also be traced between the boiling-points of compounds which do not belong to the same homologous series but show a definite structural relationship to one another. Thus an organic acid is commonly found to boil about 40° higher than the corresponding primary alcohol, and about 45° higher than its ethyl ester.

The boiling-points of the corresponding normal hydrocarbons of the series C_nH_{2n+2}, C_nH_{2n}, and C_nH_{2n-2} approximate closely to one another (*e.g.* $C_{18}H_{38}$, 181·5°, $C_{18}H_{36}$, 179°, $C_{18}H_{34}$, 184°).

In the case of isomeric substances which differ in the construction of their carbon chains, the highest boiling-point corresponds to the normal structure in which no side chains are present. As soon as side chains appear the boiling-point is lowered, and the more branched the carbon chain the greater is the difference observed.

Among regularities in the aromatic series it may be mentioned that ortho-substitution products generally have somewhat higher boiling-points than the isomeric meta- and para-compounds.

5. Solubility

Many carbon compounds are more or less readily soluble in water; for such as are not we may employ as solvents alcohol, ether, ligroin (petroleum ether), glacial acetic acid or benzene, as well as mixtures of these liquids. A selected solvent is frequently utilised in the identification, isolation or purification of a compound. Hydrocarbons are either insoluble

or very sparingly soluble in water, but if hydrogen in these compounds is replaced by oxygen or the hydroxyl group the solubility increases, and becomes the greater as more hydrogen is substituted. The first members of the homologous series of alcohols, aldehydes, ketones and acids are soluble in water, but as the proportion of carbon increases the solubility in water diminishes.

6. Density or Specific Gravity

It has already been pointed out that a simple relationship exists between the density and molecular weight of a gaseous compound (p. 13). Some regularities have also been discovered for liquid substances in connection with their molecular volume, *i.e.* molecular weight divided by specific gravity. For further information on this subject reference should be made to papers published by Traube.[1]

7. Electrical Conductivity

Since the development of the dissociation theory the property of conductivity has been frequently utilised in organic chemistry, particularly for the solution of theoretical problems. Mention may be made of the work of Ostwald and Arrhenius on the conductivity of organic acids and their sodium salts, and the later investigations of Hantzsch on substances with labile groups.

Determination of the Basicity of an Acid from the Electrical Conductivity of its Sodium Salt.—According to Ostwald,[2] the conductivity of the sodium salt affords a means of deciding the basicity of an acid, since there is a definite relationship between the molecular conductivities of the alkali salts of mono-, di- and tribasic acids, between the dilutions of 32 and 1024 litres. In the case of the sodium salt of a monobasic acid the molecular conductivity increases by 10 to 13 units between these dilutions; for a dibasic acid the increase is 19 to 25, and for a tribasic acid approximately 28 units. These differences are so considerable that they may be used to distinguish between mono- and polybasic acids. As most sodium salts are soluble in water, even when the free acids do not possess this property, the method is of great utility. It fails, however, if the acid is so weak that the salt is considerably hydrolysed in aqueous solution.

Strength of Acids and Bases. Influence of Substitution on the Dissociation of Acids.[3]—The conductivity has been found to give a measure of the strengths of acids and bases in so far that the stronger acid or base is the better conductor. On these grounds Arrhenius in 1884 suggested that the strength of an acid was proportional to its conductivity, or rather to its degree of dissociation. A corresponding relationship also holds for bases.

[1] Traube, *Ahrens Vorträge*, 1899, 4, 255. [2] *Z. phys. Ch.*, 1887, 1, 74; 1888, 2, 901; also Walden, *Z. phys. Ch.*, 1887, 1, 529; 1888, 2, 49. [3] See also Flürscheim, *J. C. S.*, 1909, 95, 718.

It has long been known that the strength of an acid such as acetic acid is increased when a hydrogen atom is replaced by chlorine. Thus monochloracetic acid, $CH_2Cl.COOH$, is distinctly stronger than acetic acid, $CH_3.COOH$; dichloracetic acid, $CHCl_2.COOH$, is stronger still; and trichloracetic acid, $CCl_3.COOH$, even more so. The same sequence is to be observed in the dissociation constants K, for which Hantzsch found the values

$CH_3.COOH$	$CH_2Cl.COOH$	$CHCl_2.COOH$	$CCl_3.COOH$
1.80×10^{-5}	155×10^{-5}	$5{,}140\times10^{-5}$	$121{,}000\times10^{-5}$.

A similar increase in acidity occurs when hydrogen is replaced by many other substituents, although methyl and amino groups diminish the value. Different substituents affect the acid strength of acetic acid in the order $NO_2>CN>COOH>Cl>Br>I>OCH_3>H>CH_3$. In the case of benzoic acid substitution in the ortho position exerts a greater influence than in the meta or para position, and the above order of groups also holds approximately for the *o*-substituted acids. The fundamental nature of the change following on substitution is shown by the fact that the same sequence of groups is often repeated in their relative effect on other properties. These *polar* regularities are sometimes of value in solving problems of constitution.

Hydrolysis.—In aqueous solution the salt of a weak acid or base undergoes a partial decomposition termed hydrolysis. A solution of aniline hydrochloride, for example, contains besides aniline hydrochloride a certain amount of free aniline and free acid, the latter of which is in addition subject to electrolytic dissociation. These constituents of the solution exist in a state of equilibrium which varies with temperature and concentration. In a similar manner a solution of sodium phenolate contains a proportion of free phenol and sodium hydroxide. Water therefore possesses the property of partially liberating weak acids or bases from their salts. The amount of hydrolysis may be determined quantitatively by conductivity measurements and a variety of other methods.[1]

In a somewhat different sense the term *hydrolysis* is employed to indicate the decomposition of esters, amides, nitriles, etc., through the agency of water (see pp. 156, 207, 211). Generally speaking, the reagents actually used in such cases are acids and alkalis which bring about the reaction with greater velocity and completeness.

8. Polar Properties of Organic Compounds

Within the last few years considerable progress has been made in our knowledge of the electrical structure of compounds, more especially with reference to the changes produced by substitution. It has long

[1] See Findlay, *Practical Physical Chemistry* (Longmans).

been usual to classify substituent groups as *electronegative* or *electropositive* in type, according to their influence upon the ionisation of acids and bases. Electronegative groups, in general, increase the dissociation constant of an organic acid, whilst electropositive groups lower the value. But it is only recently that the work of Debye, J. J. Thomson and others has enabled us to give a precise and quantitative meaning to the polarity of substituent groups. The present standpoint may be summarised briefly as follows.

The electrical centre or centre of gravity of the electrons in a molecule may or may not coincide with that of the protons. In the former case the molecule will be non-polar with respect to an external field, but in the latter case it will behave as an electrical doublet or **dipole.** If we represent the molecule diagrammatically as in Fig. 18, the positive and negative centres (or poles) may be indicated by + and − respectively, separated from one another by a distance *d*. Obviously the molecules will have a definite turning moment in an electrical field and will tend to arrange themselves uniformly in such a manner as to produce a system of minimum potential energy, a tendency which will be opposed by the heat vibration of the molecules. The magnitude of the turning moment depends upon *e* the charge at the poles and *d* their distance apart. A quantitative measure of this function is given by the **dipole moment,** μ, which may be calculated by various methods from data referring to the refractivity and dielectric constant of the compound in the gaseous state or in dilute solution in a non-polar solvent such as benzene or hexane.[1] As a result of many investigations on these lines it has been found that hydrocarbons in general have an electrical moment which is either zero or of very small magnitude. Mono-substituted hydrocarbons, on the other hand, give values of μ which are characteristic of the particular substituent present and depend only in minor degree upon the nature of the hydrocarbon radical to which it is attached. This is illustrated by the figures for derivatives of ethane and benzene given in table on p. 81, in which the signs + and − are introduced solely for the purpose of indicating the electropositive or electronegative character of the polar substituent. Further confirmation of the specific influence of the substituent is given by the work of K. L. Wolf [2] on various ketones and of Errera and Sherrill [3] on the isomeric heptanols.

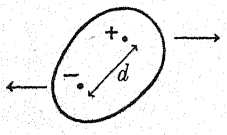


FIG. 18.

It appears that in the majority of cases, at all events, the dipole is located within the substituent group or in the neighbourhood of the bond joining it to the adjacent carbon atom. Among electronegative groupings the positive end of the dipole is directed towards the parent

[1] The external field will also tend to distort the dipole to an extent depending on the strength of the field and the deformability of the molecule. For further details reference should be made to *Polar Molecules*, by P. Debye (Chemical Catalogue Co., New York, 1928); Højendahl, Thesis (Copenhagen, 1928); *Dipole Moments*, R. J. W. Le Fevre, 1938. [2] K. L. Wolf, *Zeit. phys. Chem.*, 1929, B2. 39. [3] Errera and Sherrill, *J. A. C. S.*, 1930, **52**, 1993.

hydrocarbon radical, the reverse arrangement holding for electropositive groups.

$\overset{\delta+\ \delta-}{H_3C.Cl}$ $\overset{\delta+\ \delta-}{H_3C.NO_2}$ $\overset{\delta-\ \delta+}{H_3C.NH_2}$

The orientation of the dipole for electronegative groups was deduced, for example, from the case of a compound $R.CH_2Cl$, in which chlorine tends to separate as chloridion, Cl^-, taking with it *both* of the covalency electrons originally binding it to carbon. It is therefore assumed that in the carbon-chlorine link, the covalency electrons are normally situated in closer proximity to chlorine than to carbon (*e.g.* C :Cl) thus leading to partial charges on carbon and chlorine as indicated. This is supported by the fact that the nitro group is written with the same orientation in order that its electronic structure may conform to the requirements of the octet theory (see p. 29). Dipoles of electropositive type must therefore have the opposite arrangement.

Dipole Moments of Compounds [1]

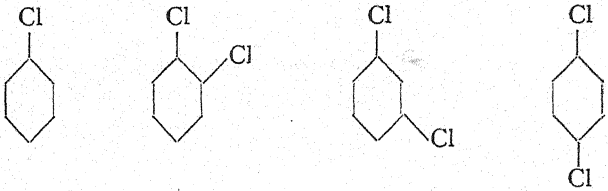
	μ		μ
$C_2H_5.NH_2$	+1·31	$C_6H_5.NH_2$	+1·5
(C_6H_{14})	0	$C_6H_5.CH_3$	+0·4
$C_2H_5.COOH$	−0·6 (?)	C_6H_6	0
$C_2H_5.O.C_2H_5$	−1·2	$C_6H_5.COOH$	−0·9 (?)
$C_2H_5.OH$	−1·7	$C_6H_5.OCH_3$	−1·2
$C_2H_5.I$	−1·7	$C_6H_5.I$	−1·25
$C_2H_5.Br$	−1·9	$C_6H_5.Br$	−1·5
$C_2H_5.Cl$	−2·0	$C_6H_5.Cl$	−1·5
$C_2H_5.CHO$*	−2·7	$C_6H_5.OH$	−1·7
$C_2H_5.CN$	−3·3	$C_6H_5.CHO$	−2·8
$C_2H_5.NO_2$	−4·0	$C_6H_5.CN$	−3·85
		$C_6H_5.NO_2$	−3·9

* By analogy with CH_3CHO.

The value of μ for a monosubstituted hydrocarbon gives a measure of the electric moment, but affords no information regarding the sign or orientation of the dipole. In some cases the latter can be deduced, as has been shown above for the chloro and nitro groups. By using these groups as standards of reference, other substituents may then be classified as electronegative or electropositive by means of the vectorial method suggested by J. J. Thomson.[2] *o*-Dichlorobenzene, for instance, has a much greater moment than chlorobenzene, because the two CCl-dipoles in this compound are arranged in such a manner as to reinforce one another. *p*-Dichlorobenzene, however, behaves in a uniform electrical field as a non-polar substance, giving $\mu = 0$. In this case the two CCl-dipoles are oriented in opposite directions and their effects cancel out.

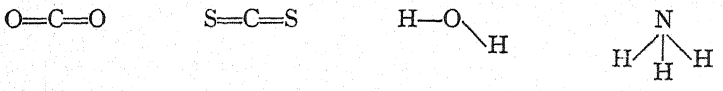
[1] The majority of these values have been determined by J. W. Williams, C. P. Smith and J. Højendahl, and are taken from Debye's *Polare Molekeln* (Leipzig, 1929). Some of the figures are subject to minor corrections. [2] J. J. Thomson, *Phil. Mag.*, 1923, **46**, 513.

Similarly, Cl and NO_2 being both of the electronegative type, it is found that among the nitro-chlorobenzenes the *o*-compound ($\mu=3\cdot78$) gives a



higher moment than the *m*- ($\mu=3\cdot18$) or *p*-compound ($\mu=2\cdot36$). Among the methyl aminobenzoates, however, where the two groups are of the opposite type, the moment is least ($\mu=1\cdot0$) in the *o*-compound, of intermediate value ($\mu=2\cdot4$) in the *m*- and highest ($\mu=3\cdot3$) in the *p*-compound in which the dipoles reinforce one another. Relationships of the same kind are found among *cis* and *trans* isomerides, *e.g.* of the types R.CH : CH.R and R.N : N.R, the *cis* forms having considerable dipole moments and the *trans* forms zero value (see azobenzene).

Molecules such as carbon tetrachloride, carbon disulphide and carbon dioxide also possess zero moment, from which it follows that they are symmetrical in structure, the last two being necessarily linear. Water and ammonia, however, give values of 1·6 and 1·5 respectively, showing



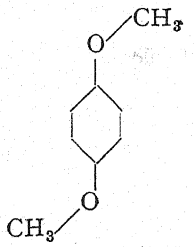
that water is not of linear type and that ammonia has a pyramidal and not a planar arrangement.

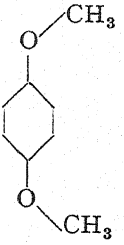
Many other apparently symmetrical compounds give finite values for μ, and in these cases the polarity has been found to arise from a non-linear arrangement of valency bonds such as occurs with divalent oxygen and trivalent nitrogen. Probably the molecules assume an unsymmetrical formation as a result of the forces of attraction or repulsion exerted by neighbouring groups on one another, or merely owing to the free rotation of the unsymmetrical substituents around the bonds uniting them to the nucleus. Thus pentaerythritol, $C(CH_2OH)_4$, and certain of its derivatives containing oxygen have been shown to possess large moments, although the corresponding bromo derivative, $C(CH_2Br)_4$, has zero value.

$C(CH_2OH)_4$	$C(CH_2OAc)_4$	$C(CH_2Br)_4$
$\mu=2$	2·6	0

The reason for this is best illustrated by reference to hydroquinone dimethyl ether. Since each methoxyl group may rotate freely about the bond joining oxygen to the carbon atom of the benzene ring, the molecule when not in the solid state must be regarded as existing in all possible forms between the two extremes I and II. Of these, structure I (*trans*)

will have zero dipole moment, whereas II (*cis*) will have a moment of appreciable magnitude. Intermediate forms also possess finite moments,

I. 

II. 

which diminish in value as the structure approaches that of I. Hence by summation of the various forms the compound possesses a definite moment, which is due to the angle between the oxygen valency bonds. A similar example is given by *p*-phenylene diamine, $H_2N.C_6H_4.NH_2$, where the moment arises from the pyramidal distribution of the nitrogen bonds.

In the following section it will be shown how information gained from the study of dipole moments has been used to explain the changes in the physical and chemical properties of compounds arising from the substitution of hydrogen by other atoms and groups.

Influence of Dipoles on the Properties of Compounds

Evidence now available shows that many properties of compounds are directly influenced by the sign and magnitude of the dipoles present in the molecule. Effects of this kind have been investigated more especially in connection with the dissociation of acids, the velocity of chemical reactions, molecular association and optical activity (see p. 95).

One general cause of molecular association in polar compounds is the orientation of dipoles in such a manner that the positive end of one is linked to the negative end of another, and *vice versa*, to form a closed system similar to that obtained by placing two bar magnets side by side with north and south poles together. An arrangement of this kind is termed **dipole-association** (see also p. 97); other and more complex formations of dipoles may also occur. The orientation of the polar groups is only loose and temporary, usually breaking down under the heat vibration of the molecules. Nevertheless it is responsible for the well-known phenomena of association, including elevation of boiling-point. In determining the value of the dipole moment this disturbing influence must be eliminated as far as possible by using data for the compounds either in a state of vapour or highly diluted by a non-polar solvent such as benzene. Under these conditions the polar molecules are so far removed from one another that little mutual interaction takes place.

Another general influence arising from the presence of a polar group is the **inductive effect.** When a polar substituent is attached to a chain of carbon atoms, induced charges of a sign similar to that of the dipole

introduced are relayed throughout the molecule. The effect is believed to operate partly through the chain and partly through space, but as we are not yet able to differentiate between these two processes they are included together in the term inductive effect. The origin of the change lies in the attraction or repulsion of the covalency electrons in the chain, due to the greater influence exerted by the nearer end of the dipole. Thus in the chain $\overset{-}{Cl}\leftarrow\overset{+}{C}H_2\leftarrow CH_2\leftarrow CH_2\leftarrow$, the nearer positive pole of the CCl-dipole attracts and displaces the electrons in the direction shown by the arrows (*electron shift*). Between any pair of adjacent carbon atoms the covalency electrons are therefore situated nearer the left hand than the right hand atom and an induced dipole of the type $\overset{-}{C}H_2-\overset{+}{C}H_2$ is set up. The induced effect diminishes rapidly as the distance from the original dipole increases but in suitable cases it can be traced as far as the third or even fourth carbon atom, after which it becomes too small for detection.

The induced effect provides an explanation for the observed rise in the **dissociation constant** of an aliphatic acid which follows the introduction of an electronegative substituent. In chloracetic acid, for example, the electron shift due to the CCl-dipole makes it easier for the electron pair binding the ionisable hydrogen atom to oxygen to pass under sole control of the latter atom, thus displacing the equilibrium in the following expression to the right and increasing the degree of dissociation in comparison

$$Cl.CH_2.COOH + HOH \rightleftharpoons Cl.CH_2.\overset{-}{C}OO + H_3\overset{+}{O}$$

with acetic acid. In a base, a dipole of electronegative type diminishes the basicity.

With electropositive groups the inductive effects are in the opposite direction to those indicated above, *e.g.* $\overset{+}{X}\rightarrow\overset{-}{C}H_2\rightarrow CH_2\rightarrow CH_2\rightarrow$. Thus a methyl group tends to reduce the strength of an acid and to increase that of a base. Ingold describes the inductive effect of the electronegative group in $X\leftarrow C$ as $-I$, and that of the electropositive group in $X\rightarrow C$ as $+I$. The relative effects of some of the commoner substituents on dipole moments and the dissociation constants of aliphatic acids are given by $NO_2 > \text{halogens} > H > CH_3$.

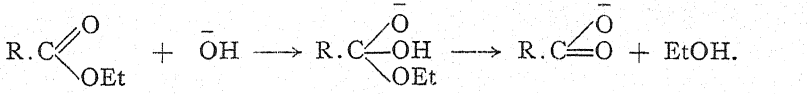
Olivier[1] has shown that the reverse sequence, $CH_3 > H > \text{halogens} > NO_2$, holds for the velocity of **hydrolysis of substituted benzyl chlorides in aqueous alcohol,** $X.C_6H_4.CH_2Cl + HOH \longrightarrow X.C_6H_4.CH_2OH + HCl$. Under the conditions employed the rate of hydrolysis depends chiefly on the speed of ionisation of the halide, a process which is facilitated by electron-repulsive (electropositive) groups and retarded by those of electron-attractive (electronegative) character.

$$X.C_6H_4.CH_2Cl \rightleftharpoons X.C_6H_4.\overset{+}{C}H_2 + \overset{-}{Cl}$$

[1] *Rec. trav. chim.*, 1923, **42**, 775.

A similar diminishing sequence is found for the velocities of reaction of a number of chemical processes, including other hydrolyses in acid media, all of which are listed together [1] as belonging to " type A."

On the other hand the sequence, NO_2>halogens>H>CH_3, holds for various other reactions which are classed as " type B." An example of this kind is given by the **alkaline hydrolysis of esters,** such as those of substituted benzoic, phenylacetic and cinnamic acids.[2] Here the effective agent in the reaction, the hydroxyl group, has its full complement of electrons and is therefore a **nucleophilic reagent,** seeking a point of attack (the positive end of the CO-dipole) at which there is a deficiency of electrons. For this reason the reaction is assisted by the presence of groups such as NO_2 which tend to withdraw electrons from the carboxylic side chain.



The *alkaline* hydrolysis of benzyl chlorides falls into the same category.[3]

As will be seen later, the inductive effect is also observed in **benzene substitution,** which usually involves an **electrophilic reagent,**[4] *i.e.* one seeking a point of attack rich in electrons. Hence, in general, the reaction proceeds more rapidly when an electropositive group is already linked to the ring, since this tends to repel electrons into the benzene nucleus, but is retarded by the presence of an electronegative group which tends to withdraw electrons. A simple inductive influence, however, is only

produced by a substituent in a saturated chain of atoms ; in a conjugated system of single and double bonds powerful effects of another character, known as *electromeric*, may be set up with substituents such as hydroxyl, which contain unshared electrons on the atom directly bound to the unsaturated system. These are discussed under benzene substitution, p. 370.

9. The Parachor [5]

For many years chemists have sought to discover an additive property of compounds which could be measured accurately and which would be independent of the temperature, the object being to make use of the values so found to obtain an insight into the constitution of the molecules. In this connection a function applying to non-associated liquids has been investigated by Sugden, who makes use of the value [P], termed

[1] See Ingold and Rothstein, *J. C. S.*, 1928, 1217 ; Williams, *ibid.*, 1930, 40. [2] Kindler, *Ann.*, 1926, 450, 1 ; 1927, 452, 90 ; 1928, 464, 278. Ingold and Nathan, *J. C. S.*, 1936, 222. [3] Shoesmith and Slater, *J. C. S.*, 1924, 125, 1312, 2278. [4] Electrophilic and nucleophilic reagents are also described as kationoid and anionoid respectively. [5] *The Parachor and Valency*, by Sugden (Routledge, 1930).

the *parachor*, calculated from the expression $[P] = M\gamma^{\frac{1}{4}}/(D-d)$, in which M represents the molecular weight, γ the surface tension, D the density of the liquid substance and d the density of the vapour. This function is independent of the temperature and, as has been pointed out by Lowry,[1] is of the nature of a molecular volume, M/D, "which has been corrected with the help of the surface tension for the overwhelming influence of an internal pressure ranging in typical cases from 1500 to 60,000 atmospheres."

Atomic Constants.—By comparing the values of the parachor for successive members of a homologous series Sugden found a mean constant difference for CH_2 amounting to 39·0. From this it is possible to calculate the parachor for carbon and hydrogen. For example, the parachor for propane, C_3H_8, was found to be 150·8, hence by subtracting $3\times CH_2 = 117$, it is evident that $2H = 33{\cdot}8$. From a number of similar determinations the average value of 2H was found to be 34·3, whence $H = 17{\cdot}1$. This agrees well with that found for liquid hydrogen, $H_2 = 35{\cdot}1$. The value for carbon, $C = 4{\cdot}8$, is deduced from CH_2-H_2. Other elements are calculated in a similar way from the parachors of *saturated* aliphatic compounds, the parachor for chlorine, for example, being obtained from the difference between $CHCl_3$ and CCl_4. By comparing saturated compounds in this manner Sugden derived a large number of constants characteristic of the different atoms.

Structural Constants.—In all saturated compounds the contribution of the single valency bond uniting the elements is assumed to be zero. This means that the single bond is chosen as an arbitrary zero level from which the effect of other structures is measured. On comparing saturated open chain hydrocarbons with those of unsaturated and cyclic types, it was found that a definite contribution to the parachor is made by each double bond, triple bond and each 3-, 4-, 5- or 6-membered ring present in the molecule. The atomic and structural parachors thus deduced may be summarised in the following table.

Atomic and Structural Parachors

C	4·8	Triple bond	46·6
H	17·1	Double bond	23·2
N	12·5	3-Membered ring	16·7
P	37·7	4- ,, ,,	11·6
O	20·0	5- ,, ,,	8·5
S	48·2	6- ,, ,,	6·1
F	25·7	O_2 in esters	60·0
Cl	54·3	Semipolar double bond	−1·6
Br	68·0		
I	91·0		

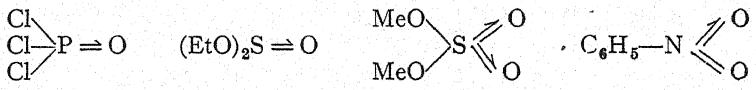
It is interesting to note that the same value for the double bond is obtained whatever the nature of the atoms linked together; thus the double bonds in ethylene, acetone, carbon bisulphide (2) and nitrosyl

[1] Lowry, *Nature*, 1930, p. 365.

chloride all approximate to 23·2 and the same value is given irrespective of whether the double bonds are conjugated or widely separated. It will be observed that the parachor for the triple bond is almost exactly double that of the double bond, consequently it does not serve to distinguish between compounds such as $CH_3O{\cdot}C \vdots N$ and $CH_3{\cdot}N : C : O$. The parachor is thus a function of a very simple type, which is made up of two series of constants, one set for the atoms and another for the linkages present in the molecule.

The parachor provided the first experimental evidence in support of Lowry's view that a double bond is not always a double covalence or a double electrovalence (see p. 28). Sugden found that among compounds formerly written with a double bond, the great majority gave a value for the double linking of +23. In some compounds, however, a small negative value of −1·6 had to be assumed. Further examination showed that the latter substances could only be formulated as containing a double covalence by breaking the Lewis octet rule and attributing to one of the atoms participating in the double bond a valency shell of ten or more electrons. In all such cases, one of the atoms still retains unshared electrons and it is possible to preserve the octet rule by formulating the double linking as a *semipolar* or mixed *double bond*. As an illustration of this point we may mention the case of trimethylamine oxide which is discussed on p. 28.

Among other compounds giving small negative values for the double bond and which are therefore supposed to contain one or more semipolar double bonds are thionyl chloride, phosphorus oxychloride, methyl sulphate, ethyl sulphite, sulphonic derivatives and nitro compounds.[1]



On the other hand, derivatives of carbonic acid, nitroso compounds and nitrites give the usual values corresponding to a non-polar double bond.

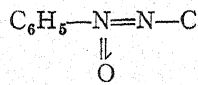
The measurement of parachor values leads to a number of conclusions of interest to organic chemists. The values for benzene derivatives, for example, are in excellent agreement with the Kekulé formula containing three normal double bonds.

C_6	$6\times4{\cdot}8$	. . . .	=	28·8
H_6	$6\times17{\cdot}1$	. . . .	=	102·6
3 double bonds	$3\times23{\cdot}2$	. . . .	=	69·6
6-membered ring	. .	. . . .	=	6·1
[P] observed	206·2	[P] calculated	.	=	207·1

Azoxy-compounds appear to have one double bond and one semipolar

[1] In the nitro group both oxygen atoms are now represented as being in the same electronic state, see pp. 29 and 88.

double bond, thus supporting the unsymmetrical formula for these compounds.

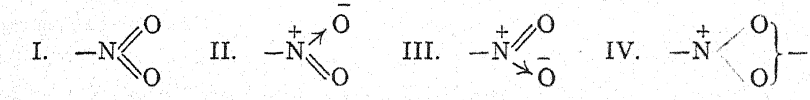


A curious anomaly is found for the oxygen value in carboxylic esters, the parachor for which is slightly less than that calculated on the usual formula. This is part of the general abnormality of the carboxyl group which is regarded as a *resonance hybrid* (see following section).

Parachor measurements have also been employed [1] as a means of determining the structure of isocyanides, the results supporting formula I in place of the bivalent carbon structure II, advanced by Nef.

10. Resonance or Mesomerism [2]

During the past few years information from a number of sources has necessitated a revision of certain organic formulæ. Reference has already been made to the case of the nitro group, originally formulated as I and later modified to II in order to bring it into agreement with parachor data (p. 87) and with the electronic theory, since nitrogen in its higher valency state has only four covalent links, the fifth being electrovalent.

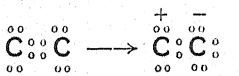
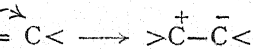


Formula II was found to be inadequate when the dipole moment of *p*-dinitrobenzene proved to be zero, thus showing that the structure is a symmetrical one. Had the nitro group contained a single co-ordinate link as in II, it would have been electrically unsymmetrical and *p*-dinitrobenzene would have resembled hydroquinone dimethyl ether and *p*-phenylene-diamine in having a moment of considerable magnitude (compare p. 83). Further confirmation of symmetry is given by the case of the closely related nitrate ion, in which X-ray and infra-red spectroscopic data show all three oxygen atoms to be in exactly the same electronic condition. According to present views, the nitro group is said to be in a **state of resonance or mesomerism,** with an actual electronic arrangement intermediate between those represented by the extremes II and III (which are known as **the unperturbed or contributing forms**) and possessing greater stability than either of these. This mesomeric structure is described as a **resonance hybrid** of forms II and III, but it must be emphasised that a definite intermediate arrangement of electrons is implied and that there is no suggestion of anything resembling an oscillation between the unperturbed forms. A consideration of formulæ II and III shows that

[1] D. L. Hammick, R. C. A. New, N. V. Sidgwick, and L. E. Sutton, *J. C. S.*, 1930, 1876.
[2] See *Modern Theories of Organic Chemistry*, by H. B. Watson (Oxford, 1941); *Physical Organic Chemistry*, by L. P. Hammett (McGraw-Hill Book Co., 1940).

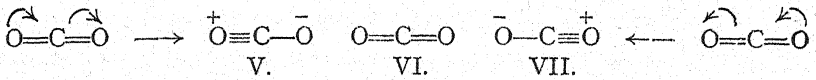
in the case of the nitro group the intermediate mesomeric state must be a symmetrical arrangement, such as is conveniently expressed in IV, which conveys the idea of a negative charge distributed over both oxygen atoms.

In any given compound the various contributing or resonating structures may be derived from each other by **electromeric displacements,** *i.e.* by changes in which electrons, whilst remaining in one octet, enter or leave another.[1] A simple example of electromeric displacement, which was first postulated by Lowry in 1923, is afforded by an ethylene derivative. A pair of electrons taking part in the double union may be supposed to be transferred bodily to one of the carbon atoms, giving it a negative charge and leaving the remaining carbon positively charged. Transfers of this kind are represented by curved arrows indicating the

 or 

direction of the change, and are assumed to be *completed* only momentarily at the time of reaction, *e.g.* during the instant preceding addition to the double bond. Whether the displacement tends to be greater in one direction or in the reverse sense will depend on other factors, including the nature of the groups attached to the carbon atoms. Ethylene itself has a symmetrical structure and the mesomeric form approximates closely to the non-polar arrangement $CH_2 = CH_2$, which is intermediate between the two polar forms derived in the above manner.

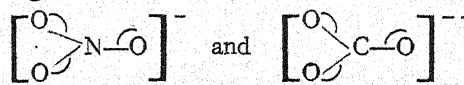
Another simple illustration of resonance is given by carbon dioxide, which may be written in the three contributing forms V, VI and VII.



V. VI. VII.

It will be seen that V and VII are derived from VI by electromeric displacements, a pair of electrons leaving the carbon octet and becoming attached to one oxygen atom, which therefore acquires a negative charge. Simultaneously the carbon octet is completed again by the movement of two unshared electrons from the oxygen at the other end of the molecule, leaving this oxygen with a positive charge (oxonium state) and attached by a triple bond in place of the original double bond.

Infra-red and X-ray spectroscopic investigations on carbonates have established the fact that in the carbonate ion as in the nitrate ion the oxygen atoms are all in the same electronic condition. The ionic structures are therefore in a state of resonance and are represented by formulæ such as the following.



The conception of resonance or mesomerism in organic compounds was introduced by Ingold,[2] and the explanation of the stability of the

[1] Ingold, *Rec. trav. chim.*, 1929, **48**, 798. [2] *J. C. S.*, 1933, 1125. *Chem. Rev.*, 1934, **15**, 225.

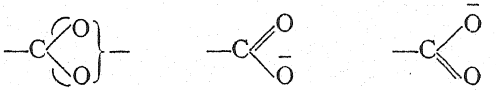
mesomeric state is due to Pauling.[1] The latter showed that resonance may be deduced from a wave-mechanical treatment, applicable to any molecule capable of being represented by two or more structures in which the positions of the nuclei are approximately the same and the energies are of the same order of magnitude, but in which the electrons have different arrangements.[2] It can then be proved mathematically that there is a state intermediate between those which are expressed by our usual formulæ, and that this possesses a minimum of energy and hence a maximum stability. In general, therefore, this intermediate or mesomeric state will be the form in which the molecule exists.

A consequence of resonance, which is well illustrated in the case of carbon dioxide, is that linkages formerly represented as double bonds may assume a character intermediate between double and single bonds. In these cases the lengths of the interatomic distances are also found to be intermediate, as has been established by investigations based on X-ray diffraction in crystals, X-ray and electron diffraction in gases [3] and Raman, infra-red and band spectra. By these methods the lengths of carbon to carbon links have been determined as follows. Single bond, 1·54 Å, in diamond, ethane, cyclohexane; double bond, 1·34 Å, in ethylene, allylene; triple bond, 1·20 Å, in acetylene. In benzene, however, which exhibits a considerable degree of resonance the hybrid bonds are each found to be 1·39 Å, and in anthracene they are 1·41 Å. A similar modification of both single and double bond lengths is found in other conjugated systems. From such data it is often possible to estimate approximately to what extent double bond character in the resonating structures has been changed into single bond character in the resonance hybrid. Any modification of structure is accompanied by corresponding alterations in the chemical properties.

Pauling has pointed out that the actual heat of formation of a compound exhibiting resonance is more than the values calculated for the corresponding contributing forms from the heats of rupture of simple covalent links. Experimental support is thus provided for the mathematical deduction that the resonance hybrid has less energy than the contributing structures and is therefore less reactive. The difference between the actual energy and that calculated for the contributing forms is termed the **resonance energy**, which is of greatest magnitude in cases where these are equivalent structures. If one of the contributing forms is of much lower energy than the others, the mesomeric state will approximate more closely to this form; the remaining forms then only make an insignificant contribution to the resonance hybrid and the chemical behaviour of the compound will resemble that of the form making the greatest contribution.

[1] Pauling and Sherman, *J. Chem. Physics*, 1933, I, 606, 679. Pauling and Wheland, *ibid.*, p. 362. Pauling, *J. A. C. S.*, 1931, **53**, 3231; 1932, **54**, 988. [2] *Cf.* H. B. Watson, *loc. cit.*, p. 59. [3] See Pauling, Brockway and Beach, *J. A. C. S.* 1935, **57**, 2705; Pauling and Brockway, *ibid.*, 1937, **59**, 1223.

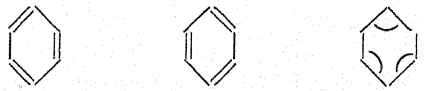
Resonance has been applied with considerable success to various problems in organic chemistry. For example, it provides a reasonable explanation of the lack of ketonic properties in carboxylic acids and their derivatives. The carboxylic ion exists in the mesomeric form VIII,



VIII IX X

which is symmetrically related to the two contributing structures IX and X. The resonance energy is therefore high and the double bond character of the carbon-oxygen link is greatly diminished. The same explanation serves for the unionised acid and for esters and amides, although here the contributing structures are dissimilar and the mesomeric form will approximate more closely to one form.

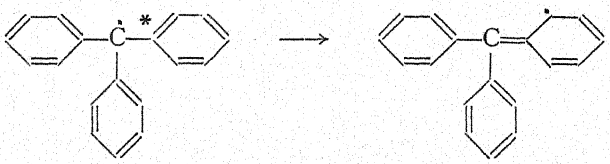
Pauling has also shown that aromatic compounds such as benzene, naphthalene and pyridine possess considerable resonance energy, thus accounting for their stability. In the case of benzene the two contributing forms are XIII and XIV, leading to the mesomeric form XV, in which



XIII XIV XV

the double bond character is greatly diminished and therewith the reactivity towards additive and oxidising agents. This rational explanation of aromatic character represents one of the triumphs of the theory of resonance. On the other hand pyrrole, with feeble aromatic properties, has only a small resonance energy. References will be found later in the text to resonance in derivatives of naphthalene, pyrazole and other compounds.

Mesomerism also explains the stability of the radical triphenyl methyl.[1] This is regarded as a hybrid of $(C_6H_5)_3C.$ and of six equivalent structures in which the odd electron from the central carbon atom is distributed over the six available ortho positions and stabilised by resonance. The change may be supposed to occur by a separation of the two electrons



constituting one link of a 1 : 2-double bond (marked *), followed by union of one of them with the odd electron on the central carbon. The other electron is retained on the ortho carbon atom of the ring. In the

[1] Hückel, *Z. Physik*, 1933, **83**, 632. Pauling and Wheland, *J. Chem. Phys.*, 1933, **1**, 362; 1934, **2**, 482.

simple radical methyl, CH_3., the possibility of such a stabilising resonance does not exist and the structure is highly unstable.

In conclusion it may be noted that the theory of resonance is still in process of development and that time must necessarily elapse before its limitations are properly understood.

11. Optical Behaviour

A. Molecular Refraction

The molecular refraction of a substance is the product of the specific refraction into the molecular weight :

$$\frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{d}$$

(where n=index of refraction, M=molecular weight, d=density).

In general it is an additive property, the molecular refraction of a compound being equal to the sum of the atomic refractions of the elements contained in it.

The following table gives the atomic refractions of some of the elements, in the one column as referred to sodium light, and in the other to the red hydrogen line :—

Element.	Sodium Light.	Red hydrogen Line.	
C	2·500	2·365	Carbon in a single bond.
H	1·051	1·103	
O′	1·525	1·506	Hydroxylic oxygen.
O″	2·211	2·328	O in the carbonyl group.
O<	1·643	1·655	O in simple ethers.
Cl	5·998	6·014	
Br	8·927	8·863	
I	14·120	13·808	
=	1·707	1·836	Double bond between two carbon atoms.
≡	...	2·220	Triple carbon linking.

The atomic refraction of nitrogen varies considerably according to the compound in which it occurs. The extreme values are 2·446 and 4·363 for sodium light, and 2·311 and 4·105 for the red hydrogen line.

From the above data it is possible to calculate the molecular refraction of a series of compounds by summation of the atomic refractions, and for the most part the values so obtained are in good agreement with those determined by experiment.

As may be seen from the table, the atomic refraction of polyvalent elements, such as carbon or oxygen, varies with the state of combination, and from the experimentally determined molecular refraction it is therefore possible to draw conclusions as to the constitution of a compound. Valuable work in this sphere has been carried out by Brühl and Auwers,

who have shown that molecular refraction and dispersion are partly additive and partly structural in character.

The molecular refraction of benzene, for example, points to the presence of three double bonds in the ring, corresponding to the formula of Kekulé. According to Brühl [1] the molecular refraction also affords a means of distinguishing between the keto and enol forms of tautomeric compounds, since the double bond of the enol form betrays itself in the characteristic value of the ethylene bond.

B. Optical Rotation [2]

The theoretical treatment of optical activity has already been given in connection with stereoisomerism, see p. 30 *et seq.*

Specific Rotation.—An exact quantitative expression of the degree of activity of a fluid or dissolved compound was made possible by the introduction of the term *specific rotation* [α].

The value of the specific rotation is given by an expression such as

$$[\alpha]^t_\lambda = \frac{\alpha \times 100}{l \times c} \quad \text{or} \quad \frac{\alpha \times 100}{l \times d \times p}$$

in which λ represents the wavelength of light employed, α = angle of rotation observed, t = temperature, l = length in decimetres of liquid traversed, c = number of grams of substance contained in 100 c.c. of the solution, d = density of solution, and p = number of grams substance in 100 grams of solution. A clockwise or dextro rotation as seen by an observer using the polarimeter is written as +, and a counter-clockwise or laevo rotation as −.

The product of the specific rotation and the molecular weight M is known as the *molecular rotation*, and is represented as follows :

$$[M] = \frac{[\alpha]M}{100}$$

In this case the hundredth part of the product is taken, in order to avoid unwieldy numbers.

Variation in the Rotation with Experimental Conditions.—Owing to the great interest aroused in stereochemical problems a considerable amount of experimental data dealing with optical rotation has gradually been accumulated. In most cases (with the exception of aqueous solutions of certain sugars) the specific rotation varies with the concentration of the solution, and frequently also with the nature of the solvent employed. Thus, for example, *d*-tartaric acid is dextrorotatory in aqueous solution but laevorotatory when dissolved in a mixture of ether and acetone.

In some instances the rotation of a freshly prepared solution of an

[1] Brühl, *Z. phys. Ch.*, 1900, **34**, 31. [2] *Cf.* Walden, "Ueber das Drehungsvermögen optisch-aktiver Körper," *Ber.*, 1905, **83**, 345; Landolt, *Das optische Drehungsvermögen organischer Substanzen und die praktischen Anwendungen derselben*, 2nd edition, 1898. T. M. Lowry, *Optical Rotatory Power* (Longmans, 1935).

active substance is found to change progressively with time, until equilibrium is finally attained. This is known as *mutarotation* and is well illustrated in the case of glucose (see glucose, p. 299). The alteration in activity goes hand in hand with an intramolecular change.

Every chemical action undergone by an active compound produces a visible change in the rotation, the magnitude and direction of which is dependent on the constitution of the active molecule, as well as on the chemical character of the reagent employed.

The greatest alterations in specific rotation which have so far been effected by chemical action on a given asymmetric carbon atom occur when certain active hydroxy compounds are treated with inorganic substances to form complexes and cyclic derivatives. In these cases the degree of asymmetry, and therewith the optical properties, are often fundamentally modified.

Example I.—The addition of alkali tungstates, molybdates and uranates, and of beryllium, titanium and zirconium compounds to certain optically active substances produces a considerable change in rotation, as illustrated in the following table :—

	$[\alpha]_D$		
	Malic Acid.	Tartaric Acid.	Quinic Acid.
In aqueous solution . . .	− 2°	+ 13·2°	− 43·1°
With ammonium molybdate .	+740	+780·0	− 66·0
„ alk. uranyl nitrate . .	−500	+265·0	−102·0

Example II.—It has been shown by Walden [1] that unexpected changes occur during the interconversion of the active malic and chlorosuccinic acids, viz. :—

(*a*) By the action of phosphorus pentachloride laevorotatory malic acid, or its ester, is converted into dextrorotatory chlorosuccinic acid, or its ester.

(*b*) Laevorotatory chlorosuccinic acid is converted by certain reagents (*e.g.* silver oxide) into laevorotatory malic acid, and *d*-chlorosuccinic acid into the corresponding *d*-malic acid. On the other hand, other reagents (potassium or ammonium hydroxide) convert *l*-chlorosuccinic acid into *d*-malic acid, and *d*-chlorosuccinic acid into *l*-malic acid. Further information on this subject is given in a later chapter (see p. 281).

This change in configuration—generally known as the *Walden inversion*—has been further investigated by Emil Fischer.[2] The cycle of changes discovered by Walden between the active malic and halogen substituted succinic acids has been extended by Fischer's discovery of the similar series of changes undergone by the α-amino and the α-halogen acids. The latter investigator also proved that the same substitution reaction may produce different optical results when small changes are made in the groups united to the asymmetric carbon atom.

The explanations of the phenomenon given by Fischer and Werner agree in assuming the formation of an intermediate product in which partial valencies are involved. Hence the Walden inversion may be closely related to the process of substitution.

An explanation based on the electronic theory has recently been advanced by J. Kenyon and H. Phillips, arising out of an investigation of the changes undergone by derivatives of *l*-β-octanol.[3]

[1] Walden, *Ber.*, 1899, **32**, 1855. [2] Fischer, *Ann.*, 1911, **381**, 123. Werner, *Ann.*, 1911, **386**, 65. See also the comprehensive survey by Walden : *Optische Umkehrungserscheinungen* (Vieweg and Son, Brunswick, 1919). [3] J. Kenyon and H. Phillips, *Trans. Farad. Soc.*, 1930, 451.

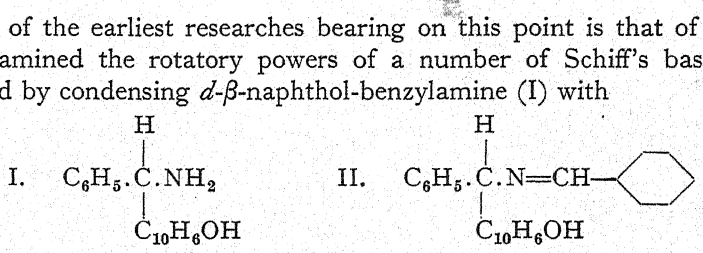
Molecular Constitution and Magnitude of Rotatory Power

Many attempts have been made to connect the constitution of an optically active compound with the magnitude of its rotation. Guye, in 1890, suggested that the rotatory power was dependent on the degree of asymmetry of the compound, as calculated from the masses of the four radicals and the distances of their centres of gravity from the asymmetric atom to which they are attached. In the same year Crum Brown advanced the hypothesis that the rotation was a function of the chemical constitution as well as of the mass of each side chain. Whilst Guye's theory proved to be untenable in the light of further research, later investigations have indicated that the same *constitutional* influences which are exhibited in properties such as inductive capacity, dissociation constants and velocity of chemical reaction are also to be observed in optical activity.

Cyclic compounds having asymmetric atoms in the ring commonly exhibit higher rotations than those of open-chain type; and the proximity to the asymmetric centre of unsaturated linkings (especially when conjugated) also tends to raise the rotatory power. An interesting constitutional regularity was discovered by Frankland and confirmed in numerous cases by Pickard and Kenyon and their co-workers. In a homologous series the smooth curve representing the rotatory powers frequently shows sudden deviations as the growing chain attains a length of 5, 10, 15, etc., atoms. This is explained on the basis of Baeyer's Strain Theory, on the supposition that the growing chain assumes a spiral formation in space, so that every increase of 5 or 6 atoms again brings the free end into the neighbourhood of the beginning of the chain. Such abnormalities are also found in other properties of homologous compounds (see pp. 357, 424, 429).

Influence of Polar Substituents contained in the Active Molecule

One of the earliest researches bearing on this point is that of Betti,[1] who examined the rotatory powers of a number of Schiff's bases (II) prepared by condensing *d*-β-naphthol-benzylamine (I) with



benzaldehyde and various substituted benzaldehydes. On introducing substituents into the benzaldehyde ring it was found that their influence on the rotatory power of the Schiff's base corresponded approximately to their effect on the dissociation constant of benzoic acid.

Similar relationships have been observed among other optically active derivatives by Rule and co-workers. The rotatory powers of the *l*-menthyl

[1] For a summary see M. Betti, *Gazz. chim. Ital.*, 1923, **53**, 424. *Trans. Farad. Soc.*, **1930**, 337.

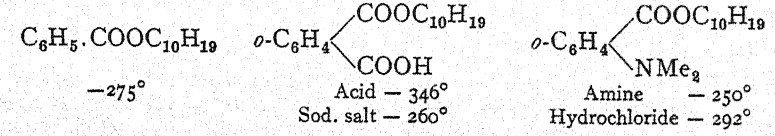
esters of monosubstituted acetic acids, for example, were found to increase with the dissociation constants k of the acids.[1] An even closer agreement is obtained by comparing the rotatory powers directly with the dipole moments (μ) characteristic of the substituent groups (see p. 80), as may be seen from the following table.[2]

Homogeneous l-*Menthyl Esters of Monosubstituted Acetic Acids,* $X.CH_2.COOC_{10}H_{19}$

X.	$\mu \times 10^{18}$.	$[M]^{20}_{5461}$.	$k \times 10^5$.
NEt_2 . . .	+1·4	−154·6°	Small
NMe_2 . . .	+1·4	156·9	,,
H	±0	157·3	1·8
CH_3 . . .	±0	160·2	1·4
COOH . . .	−0·7 (?)	160·2	160
OCH_3 . . .	−1·2	165	33
OH . . .	−1·7	165 (at 94°)	15
Br	−1·5	169	138
Cl	−1·5	171	155
CN . . .	−3·8	174	370

Polar influences of the same nature have also been traced in the molecular rotations of *l*-menthyl ethers,[3] and of the *l*-menthyl and *β*-octyl esters of substituted benzoic acids.[4]

Intimately connected with this question is the modification in rotatory power which occurs when an optically active acid or base is converted into a salt. This change frequently results in a greatly diminished rotation or even a reversal of sign. In more complex compounds the direction of the changes in rotation may be affected by the constitution of the rest of the molecule. But even in such cases it is often observed that the introduction of an electropositive group (NH_2 or NMe_2) modifies the rotatory power in the opposite sense to an electronegative group (COOH) and that on ionisation the characteristic influence is reversed. This is illustrated by the following rotatory powers, $[M]_{5461}$ (in alcohol, $c = 5$), relating to *l*-menthyl benzoate and its ortho-carboxy and ortho-amino derivatives.[5]



On the other hand, sulphonic acids are already strongly ionised in aqueous solution and undergo relatively little change in rotation on being converted into their salts.

[1] H. G. Rule and J. Smith, *J. C. S.*, 1925, **127**, 2188. [2] H. G. Rule, R. H. Thompson and A. Robertson, *J. C. S.*, **1930**, 1887. [3] H. G. Rule and H. Tod, *J. C. S.*, **1931**, 1929. [4] H. G Rule, *Trans. Farad. Soc.*, **1930**, 321. [5] H. G. Rule and MacGillivray, *J. C. S.*, **1929**, 401.

Solvent Influence

In general, the rotatory power of a dissolved substance varies with the nature of the solvent, the variations being in some cases of surprising magnitude. The task of establishing a connection between the rotatory power of the dissolved substance and the constitution of the solvent molecule has proved a difficult one, but some progress has been made by studying the problem from the polar standpoint.

In 1926 it was found that the molecular rotations of various aliphatic octyl esters were depressed by solution in solvents derived from benzene, the extent of the change being dependent upon the polarity of the medium.[1] This indication that the rotatory power may be related to the polarity of the solvent has been confirmed in a striking manner by Rule and McLean [2] in an investigation of *l*-menthyl methyl naphthalate. A few of their observed rotations are reproduced in the following table. Here

Rotatory Powers of l-*Menthyl*.*Methyl Naphthalate in Solvents*

Solvent.	$[M]_{5461}$.	$\mu \times 10^{18}$.	Solvent.	$[M]_{5461}$.	$\mu \times 10^{18}$.
$CH_3.NO_2$ . .	−219°	3·78	$C_6H_5.CN$ . .	−372°	3·85
CH_3CN . . .	239	3·05	$C_6H_5.NO_2$ . .	423	3·89
CH_3CHO . .	316	2·71	C_6H_5CHO . .	432	2·75
CH_3I . . .	336	1·66	*o*-$C_6H_4Cl_2$ . .	433	2·24
$CH_3.OH$ . .	383	1·64	$C_6H_5NH_2$ . .	443	1·60
$CH_3.COOH$ . .	423	0·75 (?)	$C_6H_5.Cl$ . .	463	1·52
CS_2	437	0	$C_6H_5.Br$ . .	466	1·50
CCl_4 . . .	563	0	$C_6H_5.I$ . .	465	1·25
$C(NO_2)_4$ . . .	651	0	$C_6H_5.OCH_3$.	466	1·25
Hexane . . .	653	0	C_6H_6 . . .	543	0
Cyclohexane . .	688	0	$C_6H_5.CH_3$ . .	546	0

also the highest rotations are given in non-polar media and the variations in rotatory power are governed chiefly by the dipole moment of the solvent.

This effect, which is exhibited by a great variety of optically active compounds,[3] is attributed to variations in the degree of association of the compound in the liquid state or in solution. An active compound may be regarded as exhibiting normal rotatory power when it exists in the unimolecular form as a gas or in high dilution in a *non-polar* solvent. Under such conditions a dipole in the molecule is able to exert its normal influence upon the rest of the structure and hence to make its characteristic contribution to the total rotatory power. When an active solute of polar type is dissolved in a *polar* solvent, however, its molecules tend to assume a definite orientation towards the solvent molecules, commonly by the attraction of oppositely charged poles to form a closed circuit (*dipole-association*, see Fig. 19). An

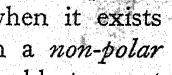


FIG. 19.

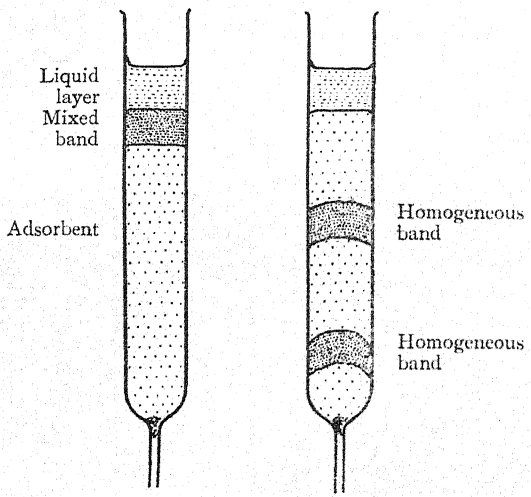
[1] H. G. Rule and R. K. S. Mitchell, *J. C. S.*, **1926**, 3202. [2] H. G. Rule and A. McLean, *J. C. S.*, **1931**, 669. Compare also Rule and J. Hill, *J. C. S.* **1931**, 2652. [3] For a summary see *Optical Rotatory Power*, Lowry (Longmans, 1935, p. 349 *et seq.*).

arrangement of this kind greatly diminishes the field exerted by the dipole (*e.g.* $\overset{+}{C}\ \overset{-}{Cl}$) upon the rest of the dissymmetric molecule to which it is attached, and so lowers its contribution to the optical rotation. If, therefore, such a solute is transferred from a non-polar solvent to a polar one, the rotatory power is displaced from the normal, and the more polar the solvent the greater is the degree of association and the greater the optical displacement.

A modification of the rotatory power in the same direction occurs if the active solute undergoes *self-association*, *e.g.* when its concentration in a non-polar medium is raised. As is to be expected, these solvent effects fall off with rise of temperature, which increases the molecular movement and in general diminishes the degree of association.

12. Chromatography

A process of the greatest value to the organic chemist for the separation of mixtures, especially of complex coloured substances, has been developed in **chromatography** or **chromatographic analysis.**[1] In this



method, which originated in the work of the Russian botanist Tswett in 1906, the mixture is dissolved in a selected solvent (*e.g.* petroleum or benzene) and the solution is allowed to flow down a vertical tube which has been firmly packed with a suitable adsorbent (*e.g.* powdered calcium carbonate or alumina) covered with the same solvent. Frequently the flow of liquid is assisted by use of gentle suction. In this way the more strongly adsorbed components of the mixture are removed from the solution to form a coloured band at the top of the tube (I).

[1] *Principles and Practice of Chromatography*, by Zechmeister and Cholnoky, translated by A. L. Bacharach and F. A. Robinson (Chapman and Hall, 1941).

The column containing the adsorbed material, which is known as the **chromatogram,** is next *developed* by washing continuously with a solvent, not necessarily the same as that used for making up the solution, when several changes normally occur. The coloured band moves slowly down the tube, spreads out and finally divides into a number of coloured bands separated by zones of white adsorbent (II). This development is due to the fact that for each component in the mixture a definite equilibrium exists between the compound in the adsorbed and dissolved states, dependent on its coefficient of adsorption. Since there is a constant flow of liquid down the tube, the adsorbed particles on passing into solution are carried a short distance downwards before being redeposited on a fresh surface of the adsorbing material. Strongly adsorbed compounds are only slowly brought into solution by the solvent, and are then rapidly deposited again. The adsorbed layer of such a compound thus travels slowly. Weakly adsorbed compounds on the other hand move rapidly. Each adsorbed compound therefore moves down the tube with a speed which is inversely related to its coefficient of adsorption, and for this reason the original mixed band eventually separates into a number of individual bands, each of which in general constitutes a chemically pure component having its own characteristic colour.

Complete separation and recovery of the components may be effected in one of two ways. The solvent may be drained off from the **developed chromatogram** and the still moist column of adsorbent extruded from the tube ; individual coloured bands can then be cut out with a spatula and the adsorbed material *eluted* by means of a suitable solvent (*e.g.* alcohol or chloroform). Or the flow of pure solvent may be continued until bands are washed out one by one from the lower end of the tube ; the various fractions are then collected separately and the solids recovered by evaporation. This second method requires a much longer time and with sensitive compounds may result in loss owing to interaction between the adsorbed material and the adsorbent.

Chromatographic analysis thus involves the following series of operations. (1) Adsorption on a selected adsorbent. (2) Development by washing. (3) Separation of the individual bands. (4) Elution of each component and recovery by evaporation. (5) In difficult cases where the bands do not separate completely the eluted products may be submitted to a second treatment.

In his original work Tswett only used exceedingly small quantities. His conclusions were drawn from the appearance of the developed chromatogram and no attempt was made to isolate or analyse the individual components. Nevertheless he was the first to show that two different chlorophylls and two different phaeophytins existed, and to suggest that leaf carotene was a mixture which might eventually be separated by the chromatographic method. Unfortunately, the principles of chromatography as published by Tswett in 1910 were written in the Russian language and for this reason did not become generally known to chemists

until 1931 onwards, in which year Kuhn, Winterstein and Lederer applied them on a preparative scale to the chemistry of the polyene pigments (see carotene).

By special devices the process has been extended to the **separation of colourless solids and liquids.** In 1934 Winterstein and Karrer independently showed that in ultraviolet light many compounds exhibit a characteristic fluorescence on the chromatogram, by means of which they may be developed and separated. Certain other colourless compounds can be converted into coloured derivatives before adsorption. Ketones, for example, yield coloured dinitrophenyl-hydrazones, which may be separated chromatographically and the hydrazone groups subsequently removed by hydrolysis. In still other cases the colourless chromatogram may be rendered visible by means of a colour reaction, *e.g.* by extruding the developed column and testing with a selected indicator. Thus mixtures of amines separated in this way are examined by lightly brushing the column of adsorbent with an aqueous solution of sulphanilic acid and sodium nitrite, when coloured streaks of bright azo-dyes indicate the positions of the individual bands. After cutting up the column, the narrow surface layer of dyestuff is scraped off each section before recovering the bulk of the adsorbed amine.

Preliminary experiments are required in order to determine the best conditions for any mixture. The adsorption coefficient depends on a number of factors, including the temperature, the chemical nature and physical state of the adsorbent and the nature of the solvent, and it is necessary that these are so adjusted that the adsorbed material is held firmly, although not so strongly as to prevent full development on washing. Among the more commonly used **adsorbents** are *alumina*, *fuller's earth*, *talc*, *gypsum*, *calcium carbonate*, *magnesia*, *lime* and *sugar*. Alumina adsorbs strongly and has been employed for a large number of separations ; sugar is a relatively weak agent. As **solvents**, *petroleum* (b.p. 60-80°) and *benzene* are most frequently used or a suitable mixture of the two. In general, organic compounds are most readily adsorbed from non-polar or very weakly polar solvents ; the final elution, on the other hand, is best effected with polar liquids.

Care must be exercised in the **preparation of the adsorption tube.** The adsorbent, having first been made up into a cream with the same solvent as that in which the mixture is dissolved, is poured in small amounts at a time into the vertical tube, the lower end of which is plugged with cotton wool. Excess liquid is usually drained off under gentle suction, accompanied by tapping of the tube. *During all these and subsequent operations the top of the adsorbent column must always remain covered with liquid.* When sufficient adsorbent has been introduced to occupy about three-quarters of the tube, it is packed down uniformly by gentle tapping with a small wooden or glass pestle, and then covered with a disc of filter paper. If the tube is evenly packed in this way and is without air bubbles, the adsorption bands have less tendency to develop irregularly.

It is quite usual, however, to find that the liquid moves more slowly in the centre of the column than at its periphery adjoining the glass surface, with the result that the lower bands assume a dome shape, as indicated in figure II, p. 98. This has to be allowed for in the final cutting up of the column.

Development by washing can often be achieved by use of the same solvent, if necessary with the addition of a small amount (1-2 per cent.) of alcohol. Benzene commonly leads to a more rapid development than petroleum, and adjustment can often be made by using mixtures of these solvents. After cutting out the individual bands, the final elution is effected by means of alcohol, chloroform or pyridine. In a few cases it may be necessary to dissolve the adsorbent in water or a suitable aqueous medium.

Chromatography has proved of the utmost value in biochemical research, for example in the separation of colouring matters of plants, of vitamins and of hormones. Many references to its use will be found throughout the course of this book. The highly selective nature of the process is illustrated by the *partial resolution of racemic* p-*phenylene-bisimino-camphor* which was carried out by Rule and Henderson [1] using a tube filled with the optically active adsorbent, *d*-lactose.

In addition to its use for the *separation of complex mixtures*, chromatography is employed in the following ways. (1) As a *test of homogeneity*: a pure compound gives a single adsorption band, which does not break up into two or more bands on washing, even when the adsorbent and solvent are changed. (2) As a sensitive *test for the identity or non-identity of two substances*: the mixed compounds if identical yield a single band. This method is particularly valuable in cases where the compounds have no characteristic melting-points. (3) For the *concentration of products* occurring at great dilution in a natural source. Koschara isolated the colouring matter uropterin from urine, in which the concentration is only 1 part in a million, by adsorption followed by elution and subsequent purification by the chromatographic method. (4) *Purification of technical preparations*.

13. Heat of Formation and Heat of Combustion

The heat of combustion of a substance is that quantity of heat which is developed during its complete combustion, and is usually quoted as the number of calories (large) per gram of substance.[2] It is of interest from the practical as well as the theoretical point of view. From it may be calculated the heat of formation and other thermochemical data, and on comparing the heats of combustion of different substances, certain constitutional regularities are observed. The calorific value of substances rich in carbon (such as coals) depends in the main on the heat of combustion.

[1] H. G. Rule and G. M. Henderson, *J. C. S.*, 1939, 1568. [2] A large calorie is the amount of heat required to warm 1 kg. of water from 15° to 16°.

Similarly, the heat of combustion is of importance in connection with food-stuffs, since these represent energy which is utilised by slow combustion in the body itself.

A special method has been devised by Berthelot for determining the heat of combustion, details of which may be found in text-books of practical physical chemistry.

Certain relationships have been established between the constitution of organic compounds and the heat of combustion. For example, an almost constant difference of 158 calories is found for each difference of CH_2 in the homologous hydrocarbons, and similar regularities may be traced in other homologous series. Among the higher members of the benzene hydrocarbons, each additional CH_2 results in an increment of approximately 155 calories to the heat of combustion.

In the aliphatic hydrocarbons the presence of a double bond raises the heat of combustion by 15·5, and a triple bond by 43·9 calories.[1] Consideration of the heat of combustion of aromatic compounds, on the other hand, leads to contradictory conclusions regarding their constitution.[2]

As an example of the application of thermochemical measurements to constitutional problems, the work of Stohmann on the heat of combustion of camphoric acid may be quoted. From the experimental data he concluded that this substance was not a derivative of tetramethylene, but either a penta- or a hexamethylene carboxylic acid. Later investigations proved camphoric acid to be derived from pentamethylene.

In general, isomeric compounds develop equal heats of combustion when they are of similar chemical character, *e.g.* methyl acetate and ethyl formate. On the other hand, if they are chemically different, their heats of combustion also differ; thus the value for methyl formate, $HCOO.CH_3$, which has carbon atoms linked through oxygen, is greater than that of the isomeric acetic acid, $H_3C.COOH$; similarly, the figure for dimethyl ether is greater than that for the isomeric ethyl alcohol.

In the case of geometrical isomers it would appear, so far as we are able to judge from the available experimental data, that the form possessing the higher melting-point, usually the *trans*-form, has the lower heat of combustion. An examination of various stereoisomeric aromatic acids has shown a complete parallel between heat of combustion and dissociation constant. Whether the isomerism is due to the presence of single or multiple bonds or to spatial configuration, it is found, with few exceptions, that the more stable form has a smaller heat of combustion and a smaller dissociation constant than the labile isomeride.[3]

The **heat of formation** of a substance is the number of calories liberated or absorbed when a gram-molecule of the compound is formed from its

[1] For further relations between the constitution and the heat of combustion of unsaturated compounds see Auwers, Roth, and Eisenlohr, *Ann.*, 1910, **373**, 239, 249, 267; *Ber.*, **43**, 1063.
[2] *Cf.* Stohmann, *J. pr. Ch.*, 1893 [2], **48**, 453. Brühl, *Ber.*, 1894, **27**, 1065. Roth and Oestling, *Ber.*, 1913, **46**, 309. [3] Roth and Stoermer, *Ber.*, 1913, **46**, 260.

elements. This value may be positive or negative. It is positive in those compounds termed *exothermic*, which are formed with evolution of heat, and negative in *endothermic* compounds produced with absorption of heat. An example of the latter class is acetylene. The numerical value for endothermic compounds is consequently written with a negative sign. The heat of formation of organic compounds is determined indirectly by subtracting the heat of combustion of the compound from the sum of the values for the individual elements.

For example, the heat of combustion of 1 gm. mol. of methane (16 gms. CH_4) is 210·8 cal., whereas that of the individual elements (12 gms. C+4 gms. H) gives a total of 232 cal.; the heat of formation of methane therefore is 232−210·8 = 21·2 cal.[1]

Nomenclature of Organic Compounds

In organic chemistry one and the same compound is frequently described with equal accuracy in a number of ways, an author employing different names as he desires to lay emphasis on the properties of the compound or on its relationship to some other substance. For the latter reason many animal and vegetable products have been named in reference to their origin, *e.g.* urea, uric acid, malic acid (from apples) and citric acid. Owing to the rapid development of this branch of science the need for a standard system of nomenclature was realised at an early stage. The position of things in 1892 was such that an international commission was called to meet in Geneva, for the purpose of deciding upon a system of nomenclature by which the constitution of an organic compound could be simply and clearly expressed. This task was only partly completed, but the findings of the Geneva commission are frequently used, more particularly in describing compounds of the fatty series.

In general, organic compounds may be referred back to one or another of a limited number of parent or index substances, from which they may be considered to be derived by replacement of hydrogen with other atoms or groups. The Geneva nomenclature is built up from the names of these parent compounds by the addition of certain syllables, such as *-ol* for alcohol, *-al* for aldehyde, *-on* for ketone and *-säure* for carboxylic acid (in English the last two become *-one* and *-acid* respectively). Unsaturated compounds take the suffix *-en* (*-ene*) for a double bond, and *-in* (*-ine*) for a triple bond. Thus ethanal is acetaldehyde, and propenol is allyl alcohol. Most of the other substituent groups are indicated in the usual manner by prefixes. In the case of compounds possessing several characteristic groups, these are named in a certain agreed sequence, and two or more of the same groups, if present in a compound, are indicated by the prefixes di-, tri- and so on. The respective positions of the substituents are shown by lettering or numbering. Unfortunately the proposals put forward have not proved suitable for adoption *en masse*,

[1] For the relationship between constitution and heat of formation of organic compounds see Brühl, *J. pr. Ch.*, 35, 181, 209.

with the result that different countries, and even different scientific publications in the same country, often show considerable variations in nomenclature. Consequently it is not possible to give here more than a brief outline of the modifications of the Geneva nomenclature at present in use. Further details will be given as each new class of compounds comes under discussion.

It will readily be understood that the Geneva practice of referring back to the simplest parent substance often leads to difficulty when applied to substances possessing several characteristic functions. For example, the compound $CHO.CH_2.CHOH.CO.COOH$ would be termed (omitting numbering) pentanolalone-acid. In modern practice therefore it has been found necessary to modify these principles and simplify matters by the use of larger index compounds, wherever these are already well known under a short name.

As may be seen from the journals of the Chemical Society and the American Chemical Society, the tendency is to employ the largest index compound available and to express the chief function of the substance in the ending.[1] Substituent radicals according to American practice are mentioned in alphabetical order, and in English after the sequence laid down by the Chemical Society. The Chemical Society uses Greek letters for all open chain compounds, the lettering commencing with the end C-atom except in the case of carboxylic acids and nitriles, when a beginning is made with the atom adjacent to the characteristic group. Isomeric open chain compounds are represented as substitution derivatives of the longest carbon chain in the formula. Ethylene homologues take the ending *-ene*, and those of acetylene *-ine*, wherever possible. The ending *-ol* is reserved exclusively for alcoholic or phenolic compounds, all others taking *-ole*, *e.g.* indole, anisole. Similarly, basic substances are indicated by names ending in *-ine*, the termination *-in* being restricted to certain neutral compounds, viz., glycerides, glucosides, bitter principles and proteins (*e.g.* palmitin, amygdalin, albumin). In Beilstein's *Lexicon* the term *oxo-* is used to describe the keto group.

Ring compounds are named in accordance with the system adopted in Richter's *Lexicon der Kohlenstoff-verbindungen*, the position of substituents being indicated by numbers. In naming substituted derivatives of compounds such as phenol, aniline or benzoic acid, the characteristic radical of the parent substance is assumed to occupy position 1.

[1] For an interesting discussion on nomenclature and indexing see A. M. Patterson and C. E. Curran, *J. Am. C. S.*, 1917, **39**, 1623.

PART I

The Aliphatic or Fatty Compounds

THE numerous compounds classified under this title may be regarded as derived from the hydrocarbon methane, CH_4, and are therefore termed methane derivatives. Since the common animal and vegetable fats similarly fall under this heading, the whole series is frequently known as the aliphatic or fatty series. Structurally, compounds of this type are distinguished by containing open carbon chains in contrast to the closed chains or rings of the aromatic or benzene series.

Organic research, which for many years had been pursued for the most part among aromatic compounds, has recently turned towards the investigation of aliphatic derivatives. New sources have been discovered for the preparation of aliphatic substances, and the growing interest in physiological chemistry has given rise to more and more work in this branch, since the chief reactions of plant and animal life are of an aliphatic nature.

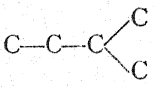
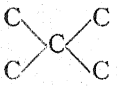
I

Hydrocarbons

I.—SATURATED HYDROCARBONS OR PARAFFINS, C_nH_{2n+2}

Nomenclature.—The homologous series of hydrocarbons possessing the general formula C_nH_{2n+2} is termed "saturated," in contradistinction to the ethylene series which exhibits pronounced additive or unsaturated properties. Not only are these compounds incapable of uniting directly with hydrogen, for example, but they are also extraordinarily resistant to attack by the majority of reagents, such as strong bases and acids, a peculiarity which has led to them being known as the paraffin series (*parum affinis*: little affinity). The names of the individual members are derived from the Greek numerals indicating the number of carbon atoms in the molecule, by the addition of the syllable -ane, *e.g.* hexane, C_6H_{14}; heptane, C_7H_{16}; octane, C_8H_{18}, and so on. Only the first four members have special names, viz., methane, CH_4; ethane, C_2H_6; propane, C_3H_8; butane, C_4H_{10}.

As already mentioned, the fourth member of the series exists in two forms, butane and isobutane, and these may give rise to different pentanes according as the carbon chain is straight as in I, or branched as in II and III.[1]

I. C—C—C—C—C II.  III. 

When a carbon atom is combined in such a manner that only one of its four valencies is satisfied by carbon, it is termed a **primary carbon atom**; similarly, if two, three or all four valencies are linked to carbon, the atom under consideration is termed **secondary, tertiary** or **quaternary** respectively. Methane, with four valencies linked to hydrogen, is an exceptional case.

Those hydrocarbons with straight carbon chains are known as *normal* hydrocarbons in distinction to the *iso*-hydrocarbons containing branched chains.

Since other compounds of the fatty series may be derived from the paraffins by replacement of one or more hydrogen atoms by other elements or groups, it has in some cases been found convenient to coin special names for the hydrocarbon residues or radicals which remain after removal of such hydrogen atoms.

Monovalent radicals, of the general formula C_nH_{2n+1}, which result from the paraffins by the removal of one hydrogen atom, are known under the general name of *alkyl* (or alphyl) groups. The name of each individual group is obtained from that of the corresponding saturated hydrocarbon by changing the end syllable -ane into -yl, *e.g. methyl*, CH_3—; *ethyl*, C_2H_5—; *propyl*, C_3H_7—. For reasons which will be seen later (p. 152) the group C_5H_{11}, instead of being called pentyl, is known as the *amyl* group.

Ethyl and **methyl** have now been shown to exist in the free state, but even at low temperatures they polymerise rapidly. In the former case the product has been identified as butane.[2] These radicals are liberated when the corresponding lead compounds, such as lead tetraethyl, $PbEt_4$, or lead tetramethyl, $PbMe_4$, are heated.

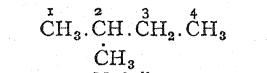
The **divalent radicals** resulting from the saturated hydrocarbons by removal of two atoms of hydrogen have the general formula C_nH_{2n}, and are named after the parent hydrocarbon by changing the end syllable -ane into -ylene, *e.g. methylene*, $CH_2{=}$; *ethylene*, $C_2H_4{=}$; *propylene*, $C_3H_6{=}$.

Similarly, the **trivalent radicals** of the general formula C_nH_{2n-1} are written with the termination -ine; *methine*, $CH{\equiv}$; *ethine*, $C_2H_3{\equiv}$; *propine*, $C_3H_5{\equiv}$.

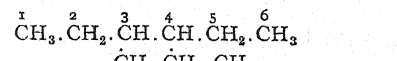
According to the Geneva proposals the names of the more complex saturated hydrocarbons are derived in the following manner. The names given above are retained

[1] The number of isomerides rises with surprising rapidity as the number of carbon atoms in the chain increases. There are five hexanes, nine heptanes and eighteen octanes theoretically possible. [2] Paneth and Lautsch, *Ber.*, 1931, 64, 2702, 2709.

for those hydrocarbons of normal straight chain constitution. The iso-hydrocarbons, containing branched chains, are regarded as alkyl substitution products of the longest straight chain hydrocarbon which it is possible to assume from the formula. In dealing with the higher members, the carbon atoms of the longest chain are numbered from one end, by which means the position of the substituting alkyl groups may be indicated. The numbering starts at that end of the carbon chain which is nearest the substituting groups. In the case where two side chains are attached to a pair of carbon atoms symmetrically situated in the main chain, the numbering commences at the end nearer the simpler side chain. In this way we obtain the following, modified to English and American practice (see also p. 104) :

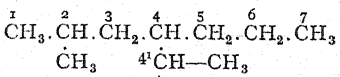


2-Methylbutane or β-Methylbutane



3-Methyl-4-ethylhexane or γ-Methyl-δ-ethylhexane.

When necessary the carbon atoms of a longer side chain are distinguished by two numbers, the first in normal type indicating the particular atom of the main chain to which the side chain is attached, and a small index number representing the position of the atoms in the latter. Those alkyl groups substituted in the side chain are then distinguished as metho-, etho-, etc., instead of methyl, ethyl, etc.



2-Methyl-4¹-metho-4-ethyl-heptane.

Occurrence and General Properties.—The homologous series of the paraffins has been investigated with few omissions from the first member methane, CH_4, to the thirty-fifth member, pentatriacontane, $C_{35}H_{72}$. After the latter, the highest known member is heptacontane, $C_{70}H_{142}$. The first four members of the series are gases under normal conditions, then follow liquids, and from $C_{16}H_{34}$ upwards they are solids at the ordinary temperature. As already mentioned, these compounds are very stable towards chemical reagents, even resisting the action of concentrated sulphuric or fuming nitric acid.[1] On the other hand, chlorine and bromine interact with comparative ease to form substitution products, from which other derivatives are readily obtainable. The boiling-points of the paraffins rise with increase of molecular weight ; among the lower members a difference of CH_2 corresponds to an increase of about 30°, the amount becoming smaller as the series is ascended.

Immense quantities of saturated hydrocarbons are found free in nature as *petroleum*, or *mineral oil*, the American variety of which consists almost exclusively of paraffins, and is a mixture of many members of the series from the lowest to the highest. *Ozokerite* or *earth-wax*, found in Galicia, is a mixture of the solid members, and products rich in paraffins are also obtained on the industrial scale by the distillation of fats and brown coal.

Until recently the dry distillation of coal was chiefly carried out in such a way that the aliphatic decomposition products first formed were,

[1] For the reaction of nitric and nitrosulphuric acids on the paraffins see Markownikoff, *Ber.*, 1899, **32**, 1441 ; Nametkin, *Ber.*, 1909, **42**, 1372.

for the most part, converted into compounds of an aromatic nature (coal tar) by subsequent contact with the glowing walls of the retort. It has been shown, however, by the work of Börnstein, Pictet, Wheeler and Franz Fischer, that in the distillation of coal by the *low temperature carbonisation process*, or under reduced pressure, the primary distillate is composed mainly of aliphatic compounds. By employing such a process on the large scale it is now possible to obtain from coal all the products characteristic of the petroleum industry. Tars of aliphatic nature are also prepared by heating coal or ordinary coal tar with hydrogen under high pressure, and by the hydrogenation of carbon monoxide in the presence of very highly active nickel and cobalt catalysts (see also pp. 115 and 377).

Methane, *marsh gas*, CH_4. *Occurrence.*—From many places in the earth's surface an issue of *natural gas* occurs, consisting of methane and other homologues of the paraffin series, together with a little admixed carbon dioxide and nitrogen. At Baku, for example, the burning gas constitutes the " holy fires of Baku," and attracted the attention of the fire-worshippers as early as 600 A.D. In America natural gas has been harnessed for lighting and the production of power. It also issues from the seams in coal-mines, where by diffusing into the atmospheric air it forms an explosive mixture (fire-damp). Methane is produced in considerable quantities, and in a comparatively pure state, by the putrefaction of organic matter and the fermentation of cellulose under stagnant water ; hence the name of marsh gas. For similar reasons (reductive fermentation of cellulose and decomposition of proteins) it is present in the intestinal gases, especially of herbivorous animals. In addition, it forms one of the chief components of coal gas.

Preparation.—Methane is obtained by the following methods :—

1. In the laboratory it is prepared by heating a mixture of sodium acetate and soda-lime. The active constituent of soda-lime in this reaction is sodium hydroxide, but the pure alkali is not used owing to its corrosive influence on the glass of the containing vessel.

$$H_3C.COONa+NaOH = CH_4+Na_2CO_3$$

2. Another laboratory method is to boil aluminium carbide with water [1] :

$$C_3Al_4+12H_2O = 3CH_4+4Al(OH)_3$$

3. By the reduction of methyl iodide with nascent hydrogen, *e.g.* by means of alcohol and the aluminium-mercury couple, or zinc and hydrochloric acid.

$$CH_3I+2H = CH_4+HI$$

The following methods are of importance from the theoretical rather than the practical standpoint.

[1] Moissan, *C. r.*, **119**, 16. Methane prepared in this way is always contaminated with hydrogen (20 per cent.) and other impurities.

4. Methane is produced together with ethylene and acetylene by the combination of carbon and hydrogen in the electric arc,[1] $C+4H = CH_4$. This reaction deserves mention since it provides a method of synthesising methane from its elements.

By the *complete synthesis* of an organic compound is meant formation from its constituent elements, or from such simpler compounds as have already been synthesised from their elements.

5. Another synthesis of methane was effected by Berthelot, by passing a mixture of hydrogen sulphide and carbon bisulphide vapour over heated copper. Carbon bisulphide and hydrogen sulphide may both be obtained from their elements, so that the synthesis may be expressed by the following equations :—

$$C+2S = CS_2\,;\ H_2+S = H_2S\,;\ CS_2+2H_2S+8Cu = CH_4+4Cu_2S$$

6. Carbon monoxide and carbon dioxide, on being mixed with hydrogen and led over reduced nickel at 250° to 300°, are both reduced to methane [2] :

$$CO+6H = CH_4+H_2O\,;\ CO_2+8H = CH_4+2H_2O$$

7. Methane is also formed by the decomposition of zinc methyl, $Zn(CH_3)_2$, or more conveniently of methyl magnesium iodide, with water.[3] Methyl magnesium iodide also interacts with ammonium chloride to give methane.

$$Zn(CH_3)_2+2H_2O = Zn(OH)_2+2CH_4$$

$$CH_3.MgI+H_2O = CH_4+Mg\begin{matrix}I\\OH\end{matrix}$$

$$2CH_3.MgI+NH_4Cl = 2CH_4+NH_2MgI+MgICl$$

Properties of Methane.—Methane is a colourless and odourless gas, liquefiable at 11° under a pressure of 180 atmospheres, and boiling at −164°. At still lower temperatures it solidifies to a crystalline mass of melting-point −186°. The gas is soluble to some extent in cold water, one litre of water at +4° dissolving 49 cubic centimetres. Methane is combustible, burning with a slightly luminous flame to form carbon dioxide and water ($CH_4+2O_2 = CO_2+2H_2O$). When mixed with air or oxygen and ignited, methane explodes violently ; dangerous mixtures of this type occur in coal-mines as fire-damp. Chlorine has no action on methane in the dark, but in diffused daylight chlorine-substituted derivatives [4] are formed, *e.g.*—

$$CH_4+2Cl = HCl+CH_3Cl.$$ Methyl chloride.

As will be seen later, these substitution products may be utilised for the conversion of methane into other compounds.

[1] Bone and Jerdan, *J. C. S.*, 1901, **79**, 1042. [2] Sabatier and Senderens, *C. r.*, **134**, 514, 689. [3] Grignard, *Ann. chim. phys.*, 1901, **24**, 438. Spencer, *Ber.*, 1908, **41**, 2302. Clarke, *J. Am. C. S.*, 1908, **30**, 1144. [4] J. Pfeifer, Mauthner and Reitlinger, *J. pr. Ch.*, 1919 [2], **99**, 239.

The presence of *methane may be detected* by treatment with ozonised oxygen, when it is converted into formaldehyde. Even small amounts of the latter are readily identified by its characteristic reactions.

$$CH_4+2O_3 = CH_2O+H_2O+2O_2$$

Ethane, $H_3C.CH_3$, is found dissolved in petroleum, and escapes from the earth's surface in many places (*e.g.* North America).

It may be prepared by the general methods given above. From a theoretical point of view, the discovery of Kolbe [1] in 1848, that ethane was formed by electrolysis of a concentrated solution of potassium acetate, is of great importance. The discharged acetanions at the anode interact with one another under the conditions of experiment to give ethane and carbon dioxide. At the cathode the discharged potassium ions react with water to form hydrogen and potassium hydroxide.

$$\begin{matrix} H_3C-CO_2K \\ \vdots \\ H_3C-CO_2K \end{matrix} +2H_2O = \begin{matrix} H_3C \\ | \\ H_3C \end{matrix} +2CO_2+2KOH+H_2$$

This is the first and most typical of those synthetic reactions which organic chemistry owes to electrolysis. Wurtz carried the process a step further by electrolysing a mixture of the salts of two fatty acids, and so by the combination of two different electrolytic residues synthesised higher hydrocarbons.

A technical preparation of ethane is based on the combination of ethylene and hydrogen in the presence of finely divided nickel, at high temperature and pressure.[2]

Ethane is a colourless, odourless gas, which burns in air with a feebly luminous flame; its critical temperature is $+34°$ and critical pressure 50 atmospheres. It is very little soluble in water but more so in alcohol. Chlorine and bromine readily react with it to give substitution products.

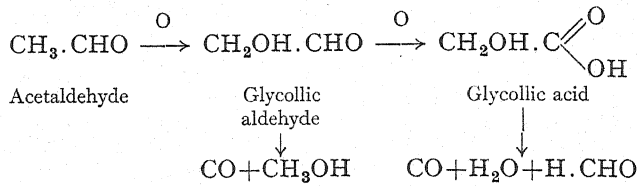
Slow Combustion of Hydrocarbons.—An extended investigation of the "slow combustion" of methane and ethane when heated with oxygen at high pressure and relatively low temperatures has been carried out by W. A. Bone and his co-workers.[3] The results show that under these conditions oxidation proceeds by successive stages of hydroxylation (H $\longrightarrow$ OH). Thus with a mixture of ethane (9 mols.) and oxygen (1 mol.) at 273° and under 100 atmospheres pressure, it was found possible to follow quantitatively the conversion of ethane into carbon dioxide, the intermediate products such as ethyl alcohol, acetaldehyde and acetic acid being identified and estimated. The main stages of the reaction are summarised below.

$$CH_3.CH_3 \xrightarrow{O} CH_3.CH_2OH \xrightarrow{O} [CH_3.CH(OH)_2] \xrightarrow{O} H_2O+CH_3.CHO \xrightarrow{O} CH_3.C(=O)OH$$

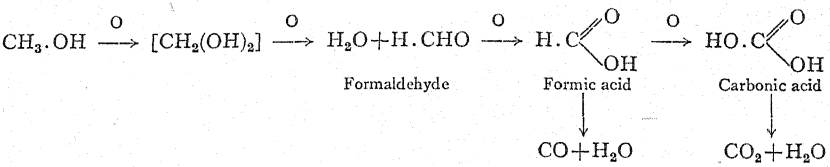
Acetaldehyde is assumed to undergo further hydroxylation to form

[1] Kolbe, *Ann.*, 1848, **69**, 279. [2] C. Sprent, *J. S. C. I.*, 1913, **32**, 171. [3] W. A. Bone, *J. C. S.*, 1933, 1601. D. M. Newitt and A. E. Haffner, *Proc. Roy. Soc.*, 1932, A, **134**, 591. Newitt and Bloch, *ibid.*, 1933, A, **140**, 426.

glycollic aldehyde and glycollic acid, each of which may decompose at the temperature of reaction to yield simpler products.



Finally, by a continuation of the same process, methyl alcohol and formaldehyde are oxidised to carbon dioxide.



There is reason to believe that this mechanism of hydroxylation is also operative in a number of other types of oxidative reactions.

Higher Homologues of Methane

For the preparation of higher homologues of the paraffin series, modifications of the methods 1, 3 and 7 given on pp. 108, 109 may be employed. The best general method is perhaps the decomposition of alkyl magnesium halides with aqueous ammonium chloride, which yields the hydrocarbons directly in the pure state. In addition, the following special methods are available :—

(a) *Synthesis from lower halogenated derivatives*, $C_nH_{2n+1}X$, by treatment with metallic sodium (*Wurtz* reaction), zinc (*Frankland*) or finely divided silver. Unsaturated hydrocarbons of the ethylene group are often formed at the same time.

$$2C_2H_5I+2Na = C_2H_5.C_2H_5+2NaI$$

These reactions proceed most readily with the iodo-derivatives and occur through the intermediate formation of metallic alkyls or of the unstable free alkyl radicals.

(b) *From unsaturated hydrocarbons*, by passing them in the gaseous state mixed with hydrogen over a suitable heated catalyst such as finely divided nickel, platinum or palladium. The two last named catalysts will also bring about hydrogenation at ordinary temperatures. For further details see p. 119.

(c) *Reduction of alcohols, aldehydes, ketones and carboxylic acids*, by heating with hydriodic acid and red phosphorus. In this manner alcohols are first converted into the corresponding iodides, which then react with more hydriodic acid and are reduced to hydrocarbons. The

iodine so liberated combines with the red phosphorus to form PI_3 and this reacts with water produced in the first stage to regenerate more hydriodic acid.

$$C_nH_{2n+1}OH+HI \longrightarrow C_nH_{2n+1}I+H_2O$$
$$C_nH_{2n+1}I+HI \longrightarrow C_nH_{2n+2}+2I$$

Higher carboxylic acids readily yield hydrocarbons by this method.

$$C_nH_{2n+1}\cdot COOH+6HI = C_nH_{2n+1}\cdot CH_3+2H_2O+3I_2$$

(d) Distillation of coal, lignite or wood at comparatively low temperatures (see pp. 108, 115).

Mineral Oil, Petroleum

Occurrence and Formation.—Petroleum is found in many places, of which the most important, from an industrial point of view, are Oklahoma and Pennsylvania in North America, the region in Caucasia having Baku as its centre, and Persia. In addition, it occurs on a considerably smaller scale in Galicia, Roumania, Hungary and numerous other parts.

With regard to the occurrence of these immense deposits, the opinion was long ago advanced by Mendeleéf that they were formed by the action of water on metallic carbides present in the hot interior of the earth, a view which appeared to be supported by subsequent work of Moissan. This hypothesis, however, is incompatible with the geological occurrence of natural gas and oil, which are never present in the hot springs rising from deep within the earth. The later discovery that the distillation under pressure of fats, such as fish oil, resulted in the formation of a product strongly resembling American petroleum, led Engler to suggest that petroleum originated from the fatty remains of marine organisms. More recently, Treibs [1] has isolated from various samples of petroleum a number of porphyrins, some of which are related to chlorophyll and others to haemin. It is therefore concluded that both plant and animal remains play a major part in the formation of petroleum deposits, and this organic source is further indicated by the presence of optically active compounds and of quinoline derivatives. The present view is that these microscopic organic remains were deposited as ooze on the beds of swamps and seas in primeval times. Further successive layers formed throughout the ages sealed them from contact with air and incorporated them in the earth's crust, where they were subjected to intense pressure and probably to an appreciable rise in temperature. Under these conditions the fossil remains decomposed, the proteins, carbohydrates and to a lesser extent the fats gradually breaking down to form petroleum. The oil tapped by the mining engineer is usually a large accumulation which has collected between the grains of an underground sand bed or more rarely in the cracks of limestone rock.

Composition.—Petroleum consists of a mixture of hydrocarbons whose composition varies with the place of origin, and which may contain members of the paraffin series together with cycloparaffins and hydrocarbons of aromatic nature. To isolate from this mixture a constituent of homogeneous composition is a task of considerable difficulty, and rarely attempted in industry.

[1] A. Treibs, *Ann.*, 1934, **509**, 103; **510**, 42; 1935, **517**, 172; **520**, 144.

The *Pennsylvanian oil* is a dark green liquid which appears reddish brown by transmitted light. It contains about twenty different hydrocarbons, and according to the researches of Markownikoff there are, in addition to the normal members, isoparaffins of the general formulæ $R_2CH.CHR_2$, CHR_3, and CR_4. The lower paraffins are contained in such proportion that inflammable vapours are given off even at low temperatures. There are also present small amounts of hydrocarbons of the benzene series (cumene and mesitylene) and their reduction products, as well as traces of organic acids and sulphur compounds. Occasionally sulphur compounds are found in larger proportion. On the other hand, the *Caucasian oil* contains about 80 per cent. of higher boiling cyclic hydrocarbons of the general formula C_nH_{2n} (naphthenes), together with lower boiling cyclohexane and cyclopentane. Oil from Borneo contains considerable amounts of aromatic hydrocarbons.

Refining of Petroleum.—The liquid is warmed to expel dissolved gases such as methane, and then distilled, the following three fractions being collected :—

(a) **Naphtha** or **benzine,** boiling-point 40° to 150° (pentanes to nonanes in American oil).

(b) **Illuminating oil** or **kerosene,** boiling-point 150° to 300° (chiefly decanes to hexadecanes in American oil).

(c) The **heavy oil** boiling above 300°, which partly solidifies on cooling. Tar and pitch remain behind in the still.

The crude illuminating oil is purified further by the addition of a little strong sulphuric acid and agitation with compressed air. After removing the layer of sulphuric acid and tarry products, the process is repeated with aqueous sodium hydroxide and again with water; the oil is then redistilled. When the removal of sulphur is necessary this is effected by heating with metallic oxides, such as copper and iron oxide, which are thereby converted into sulphides. The product so obtained is generally known as **petroleum** and is suitable for lighting and heating.

Many risks are attached to the use of insufficiently purified oil for lighting purposes, particularly if lower boiling constituents (naphtha) are present. In order to decide whether an oil is suitable for burning in lamps it is usual to determine its flash-point, by warming the oil in a special apparatus and finding by experiment the temperature at which the vapour above the liquid is inflammable. The lowest flash-point permissible in Great Britain is 73° F.

It is to be noted that only one fraction of the oil is used for lighting, the others being utilised in a variety of ways.

Naphtha is generally rectified again to yield several volatile fractions, which are collected as follows :—

Petroleum ether or **gasoline,** distilling about 50° to 60°, consists chiefly of pentane and hexane; it may be used for illumination in specially constructed lamps.

Benzine, distilling about 70° to 90°, contains a large proportion of hexane and heptane, and should not be confused with benzene from coal tar. It is used for the dry cleaning of all kinds of material.

Ligroin, distilling about 90° to 120°, like the foregoing fractions, is extensively used as a solvent for fats, oils and resins.

The heavy oil which distils above 300°, partially decomposing in the process, is also of commercial value. From it is prepared **lubricating oil** for machinery. Unlike the fatty oils, which decompose in the course of time and then attack the metal, these petroleum oils are stable in air and therefore preferable as lubricants. Many of them are even more valuable than the illuminating oils. Another product obtained from heavy oil is **vaseline,** or **petroleum jelly.**

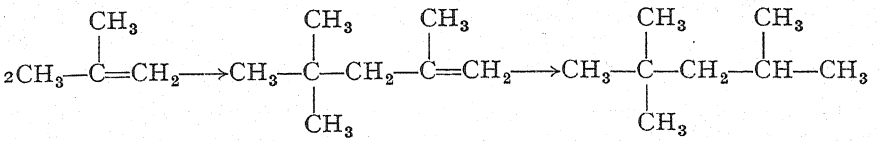
Cracking Processes.—In general, the various fractions obtained from a natural petroleum are not in such proportions as correspond to industrial requirements, motor fuel in particular being in very great demand. Fortunately, an excess of a less valuable fraction can be used to increase the amount of fuel oil, for example, by submitting it to " cracking." This may be a *thermal process* (pyrolysis) in which it is run through strongly heated iron tubes, when a considerable break-down and re-synthesis of the molecules take place. The resulting mixture ranges from gases to coke and on fractionation yields an appreciable amount of fuel oil, which is all the more valuable because it contains a high percentage of unsaturated, aromatic and naphthene hydrocarbons, which confer upon it anti-knock properties. A *catalytic cracking process* using an activated hydrated aluminium silicate has recently been introduced, which brings about much less drastic molecular rearrangement and also gives a product of high octane value.[1]

Octane numbers were introduced in 1929 in an attempt to classify fuels with respect to their " anti-knock " properties. *n*-Heptane and iso-octane are taken as standards, the former being rated as zero and the latter as 100. The rating of any fuel is expressed in terms of the octane number, *i.e.* the percentage by volume of iso-octane in a mixture of iso-octane and *n*-heptane which has the same tendency to knock under stated conditions in a standard engine as has the fuel under test. It has been found that the normal straight-chain paraffins are the worst fuels for producing knocking, and that unsaturated compounds, and especially aromatic mixtures, produce least. Hence the value of fuels obtained by cracking, since these contain iso-hydrocarbons as well as unsaturated and aromatic types. By the addition of small quantities of an anti-knock compound such as *lead tetraethyl* the octane number of a fuel can be further raised, and values well over 100 can now be obtained.

Iso-octane is prepared in large quantities by polymerisation of the isobutylene present in natural or refinery gases. In the first instance

[1] For a description of recent developments in the petroleum industry see J. Dudley Williams, *Chem. and Ind.*, 1941, 22.

di-isobutylene is formed, which is then hydrogenated catalytically to iso-octane. In a similar manner the unsaturated gases produced in



Isobutylene Di-isobutylene Iso-octane.

considerable amounts during the cracking processes are also polymerised and hydrogenated to yield valuable motor fuels.

Low Temperature Distillation of Coal.—It has already been mentioned that by varying the conditions under which the dry distillation of coal is conducted we may obtain tars of different compositions. The typical constituents produced by the low temperature process (350° to 500° C.) are naphthenes and highly viscous oils.[1] Under these conditions benzene is either absent or present in traces only, its place being taken by benzine (petroleum ether, etc.). Since large yields of tar may be obtained by this process on the technical scale, it should eventually be possible to prepare petroleum hydrocarbons in quantity from coal. As yet it is only remunerative where the cheap and readily accessible brown coal is used.

Direct Synthesis of Petroleum Hydrocarbons.[2]—It has long been known from the experiments of Sabatier and Senderens on the catalytic reduction of carbon monoxide under ordinary pressure, that the final product of reaction is methane. Fischer and Tropsch found that the use of a catalyst containing metallic iron and zinc oxide led under ordinary pressures to the formation of a mixture of methane and its higher homologues in place of pure methane. A series of catalysts were subsequently discovered which were even more active than the above iron-zinc oxide mixture. For example, carbon monoxide passed over cobalt mixed with chromium oxide at a temperature of 270° yields not only gaseous homologues of methane, but fluid and solid members of the paraffins, *i.e.* benzine and other valuable products of the type of petroleum. Reference may also be made to the use of catalysts under high pressures, by which means carbon monoxide may be converted into methyl alcohol (see p. 145) and its higher homologues (*Synthol*).

In another process invented by Bergius, coal or the higher boiling fraction of coal tar is heated with hydrogen at pressures of 275 atmospheres or upwards in the presence of catalysts of the tin or molybdenum series. This method gives about 5 per cent. of lubricating oil, and up to 50 per cent. of benzine and Diesel motor oils,[3] and appears to be of considerable industrial value. The plant required, however, is expensive and the catalyst difficult to recover. A British process involves a combination

[1] F. Fischer and Gluud, *J. S. C. I.*, 1919, **38**, 563 A. [2] F. Fischer and Tropsch, *Ber.*, 1926, **59**, 830, 923. Fischer and K. Meyer, *Ber.*, 1934, **67B**, 253. [3] A. Spilker, *Zeit. f. ang. Ch.*, 1926, **39**, 997.

of coal and coal oil distillation together with "cracking," and yields a good quality of petroleum containing a large percentage of motor spirit.

Paraffin Wax, Ceresine

A product of composition similar to that of the naturally occurring petroleum may also be obtained artificially by the dry distillation of peat, lignite, boghead, cannel coal or bituminous shale.

In the paraffin industry in Scotland bituminous shale is largely used for this purpose, and in Germany the deposits of brown coal are utilised. The material is distilled by a continuous process in long vertical retorts constructed of iron and fireclay, yielding ammonia, inflammable gases and tar. The latter after purification by washing with concentrated sulphuric acid and caustic soda (to remove creosote oil) is redistilled and separated into four fractions: naphtha, paraffin oil, lubricating oil and paraffin wax. Besides these, a product resembling asphalt may be left behind in the retort.

Paraffin wax so obtained consists chiefly of higher members of the saturated hydrocarbons, together with those of the ethylene series (p. 117), and according to its composition varies somewhat in appearance, melting-point and boiling-point. The solid hydrocarbons, beginning with $C_{19}H_{40}$, separate in large transparent leaves: higher in the series they become translucent and granular: still higher they are opaque and wax-like solids. The melting-points range from 31° to 110° and the boiling-points from about 300° upwards.

As has already been shown by numerous investigations into the low temperature coking process, ordinary coal may also yield products of the nature of paraffin wax on dry distillation, and it has recently been demonstrated that solid paraffin is a typical constituent of the low-boiling tar produced in this manner.

Reference has been made on p. 107 to the occurrence of solid paraffins and isoparaffins in nature. One of the most important deposits of this kind is the **ozokerite** or earth-wax of eastern Galicia. The more or less solid product varies from yellow to black in colour, and is found in layers from 20 to 100 metres below the surface. The raw material is refined by melting out from earthy impurities, and the brownish product is treated with caustic soda and sulphuric acid, decolorised by charcoal, and finally bleached. The resulting wax-like substance is known as **ceresine.**

Uses.—Among the different paraffin waxes those which are hard enough are employed, either alone or admixed with the higher fatty acids, in the manufacture of candles. Softer varieties are utilised in the match industry, for waterproofing fabrics and for dressing leather.

Asphalt or mineral pitch has been known from earliest times (Trinidad, Cuba, West Indies, Alsace), and is an oxidation product of the higher boiling constituents of petroleum. It is used in the manufacture of black varnishes, as a protective paint, as insulating material and in large amounts for the paving of roads.

II.—UNSATURATED HYDROCARBONS

Nomenclature of the Open-chain Unsaturated Hydrocarbons

Those hydrocarbons containing one double bond are named after the corresponding saturated compounds by changing the termination -ane into -ylene, or according to the Geneva proposals into -ene. Should two or more pairs of doubly linked carbon atoms be present, this is indicated by the ending -diene, -triene, etc. The position of the double bond is shown by prefixing the letter or number of the first atom of the doubly bound pair, *e.g.* :—

$H_2C : CH_2$ — Ethylene or ethene

$H_2C : CH.CH_2.CH_2.CH : CH_2$ — Diallyl or $\alpha\epsilon$-hexadiene.

If the double bond occurs between a carbon atom of the main chain and one of the side chain, the name of the main chain takes the termination -ane and that of the side chain -ene.

$H_3C.CH_2.C(:CH_2).CH_2.CH_3$ — γ-Methene-pentane.

$H_3C.CH_2.CH_2.C(:CH.CH_3).CH_2.CH_2.CH_3$ — δ-Ethene-heptane.

If the double bond occurs in the side chain the name of the latter takes the termination -enyl.

$H_3C.\overset{\alpha}{C}H_2.\overset{\beta}{C}H_2.\overset{\gamma}{C}H_2.\overset{\delta}{C}H.\overset{\epsilon}{C}H_2.CH_2.CH_2.CH_3$
$\quad\quad\quad

The nomenclature of the olefins is discussed above, but simpler compounds are frequently designated as substituted ethylenes :—

$H_3C.CH:CH.CH_3$	$(H_3C)_2C:CH_2$	$(H_3C)_2C:C(CH_3)_2$
Symmetrical dimethyl ethylene	Unsymmetrical dimethyl ethylene	Tetramethyl ethylene.

The structural formula for ethylene might be written either as I or II, both of which represent the carbon atoms as tetravalent. Of these

I. $H_2C=CH_2$ II. $-CH_2-CH_2-$

alternatives the former is adopted for the following reasons. If structure II containing two free valency bonds were correct, we should expect that ethyl, CH_3-CH_2-, with one free bond would resemble ethylene in being a stable compound. This, however, is not the case. The ethyl radical can be prepared, but it is exceedingly reactive and has only an ephemeral existence under ordinary conditions (see p. 106). Molecular models of type I possess a certain rigidity of structure, which is in agreement with the properties of ethylene derivatives, as illustrated by the existence of stable *cis* and *trans* isomerides such as fumaric and maleic acids. On the other hand, each half of the molecule according to formula II rotates freely about the central single bond, as in the case of ethane derivatives. This structure should not give rise to *cis* and *trans* isomerism.

Properties.—In their physical properties the olefins closely resemble the paraffins. The lower members from C_2H_4 to C_4H_8 are gases, the intermediate ones are liquids and the highest are solids. They burn with a smoky and very luminous flame. The boiling-points of corresponding hydrocarbons of the two series lie very close together, but the melting-points of the olefins are a little lower than those of the paraffins. Most of the olefins are readily soluble in alcohol and practically insoluble in water. For the lower members the specific gravity at the melting-point is 0·63, and rises with increasing molecular weight to the neighbourhood of 0·79.

In their chemical behaviour, which differs very considerably from that of the paraffins, the most characteristic property is that of addition. The double bond in these hydrocarbons is capable of taking up two monovalent atoms or groups, becoming converted into a single bond, with the formation of paraffins or their substitution products. These additive properties are found also in other classes of compounds and may therefore be treated a little more fully at this stage.

By union with hydrogen the olefins are transformed into paraffins of the same number of carbon atoms :—

$$\underset{\text{Ethylene}}{H_2C:CH_2}+H_2=\underset{\text{Ethane.}}{H_3C.CH_3}$$

The addition of hydrogen to ethylene hydrocarbons used to be carried out by heating with hydriodic acid and phosphorus, but is now effected

more rapidly and conveniently by **catalytic hydrogenation.** Sabatier, Senderens and Mailhe found that hydrogen adds on directly to unsaturated compounds at a high temperature in the presence of finely divided nickel,[1] and the same change may be induced even more readily, without the addition of external heat, by the catalytic action of finely divided platinum or palladium.[2] A detailed study has also been made of the reduction of unsaturated compounds, including ethylene, by gaseous hydrogen in the presence of colloidal palladium.[3] The results show that ethylene may be reduced to ethane at the ordinary temperature by treating equal volumes of ethylene and hydrogen with an aqueous solution of colloidal palladium. The hydrogenation is effected by the palladium hydrosol, which in the presence of hydrogen is converted into palladium hydrogen hydrosol, the latter then transferring its hydrogen to the dissolved ethylene. The reaction proceeds as long as ethylene and hydrogen are both present in the mixture.

In general, catalytic hydrogenation finds frequent application in laboratory and factory for the reduction of unsaturated organic compounds with gaseous hydrogen (see hardening of fats, p. 202).

Olefins readily unite with chlorine, bromine, iodine and iodine chloride to form dihalogen derivatives. Of the three halogens, chlorine is the most reactive and iodine the least.

$$H_2C:CH_2+Br_2 = CH_2Br.CH_2Br$$

Ethylene dibromide.

The addition of hydrogen halides, of which hydriodic acid is the most reactive, leads to the production of alkyl halides. In this reaction, if it is possible for the addition to take place in more than one way, the halogen usually attaches itself to that carbon atom which is united to the smaller number of hydrogen atoms (*Markownikoff rule*).

$$H_2C:CH_2+HI = H_3C.CH_2I$$

Ethyl iodide.

$$\begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>\!C:CH_2+HI = \begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>\!CI.CH_3$$

Isobutylene (β-methyl-propylene) — Tertiary butyl iodide (β-iodo-β-methyl-propane).

Although the Markownikoff rule holds generally for combination with hydriodic acid, many conflicting results have been reported for the addition of hydrogen bromide to olefins and especially to unsaturated halides of the type of allyl bromide, $CH_2:CH.CH_2Br$, and vinyl bromide, $CH_2:CHBr$. Recent investigations by Kharasch [4] have shown that the *pure* compounds react normally with hydrogen bromide according to the above rule, but that the direction of the addition is reversed either

[1] Sabatier and Mailhe, *J. C. S.*, 1907, A, i., 458, 488, 490, 549, 747. [2] Willstätter and Mayer, *Ber.*, 1908, **41**, 1475. [3] Paal, *Ber.*, 1909, **42**, 2239. Stark, *Ber.*, 1913, **46**, 2335. [4] M. S. Kharasch and F. R. Mayo, *J. A. C. S.*, 1933, **55**, 2468; Kharasch and M. C. McNab, *ibid.*, p. 2531. Kharasch, *ibid.*, 1934, **56**, 712.

in the presence of a peroxide such as benzoyl peroxide or in some cases merely on bubbling air or oxygen into the olefinic compound before use, which is sufficient to generate traces of peroxide. This reversal is known as the *peroxide effect*. Since allyl bromide usually contains traces of peroxide formed in contact with air, it behaves abnormally unless it is purified before use or the reaction is carried out in the presence of an antioxidant (*e.g.* diphenylamine or hydroquinone) which destroys the peroxide. With the still more sensitive vinyl bromide and vinyl chloride an antioxidant is essential for the normal reaction to take place. Olefinic hydrocarbons appear to be less sensitive and with them addition generally occurs normally unless a peroxide is added. Owing to its strong reducing action hydrogen iodide always yields the normal product, even in the presence of peroxides.

Aqueous hypochlorous acid converts the olefins into chlorohydrins (see also p. 243), in which case the hydroxyl group links itself preferably to the less hydrogenated carbon atom. Similar results are obtained with dilute chlorine water or bromine water [1] (Read).

$$CH_2 : CH_2 + HO.Cl = \underset{\text{Ethylene chlorohydrin.}}{HOCH_2.CH_2Cl}$$

$$\underset{\text{Isobutylene}}{(H_3C)_2C : CH_2} + HO.Cl = \underset{\text{Isobutylene chlorohydrin.}}{(CH_3)_2C(OH).CH_2Cl}$$

The olefins also combine directly with nitrogen trioxide, nitrogen dioxide, nitrosyl chloride and nitrosyl bromide to form respectively nitrosites, nitrosates, nitroso-chlorides and nitroso-bromides, *e.g.*

$$\underset{\text{Tetramethyl ethylene}}{(CH_3)_2C : C(CH_3)_2} + NOCl = \underset{\substack{\text{Tetramethyl ethylene} \\ \text{nitroso-chloride.}}}{(CH_3)_2C(Cl)—C(NO)(CH_3)_2}$$

With concentrated sulphuric acid the olefins yield alkyl-sulphuric acids, also known as alkyl hydrogen sulphates, the acidic radical (*cf.* addition of hydrogen halide) attaching itself to that carbon atom united to the smaller number of hydrogen atoms [2]:

$$H_2C : CH_2 + \begin{matrix} HO \\ HO \end{matrix}\!\!>\!SO_2 = \underset{\text{Ethyl-sulphuric acid.}}{H_3C.CH_2.O.SO_2(HO)}$$

$$\begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>\!C : CH_2 + \begin{matrix} HO \\ HO \end{matrix}\!\!>\!SO_2 = \underset{\text{Isobutyl-sulphuric acid.}}{\begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>\!C(OSO_3H)—CH_3}$$

[1] J. Read and co-workers, *J. C. S.*, 1920, 1214; 1922, 989; 1928, 745. For a critical discussion of methods of forming ethylene chlorohydrin see Frahm, *Rec. trav. chim.*, 1931, 50, 261.

[2] This reaction serves also for the separation of olefins from paraffins, the latter being scarcely affected: see Worstall, *J. Am. C. S.*, 1899, 21, 245.

On boiling the alkyl-sulphuric acids in aqueous solution they decompose to form an alcohol and sulphuric acid :

$$C_2H_5O.SO_2.OH+HOH = C_2H_5OH+HO.SO_2.OH$$

In this manner it is possible to effect the indirect addition of the elements of water to the olefins, converting them into alcohols.

$$H_2C:CH_2+HOH = H_3C.CH_2OH$$

Ethylene combines with fuming sulphuric acid to yield β-hydroxyethyl-sulphonic acid (*isethionic acid*), and with concentrated nitric acid to form β-nitroethyl alcohol.[1]

$$\underset{\text{Ethylene}}{H_2C:CH_2}+HO.NO_2 = \underset{\beta\text{-nitroethyl alcohol.}}{HO.CH_2.CH_2.NO_2}$$

The olefins are very easily oxidised. Dilute alkaline permanganate solutions are rapidly decolorised by them, and the olefin converted into a dihydric alcohol.

$$H_2C:CH_2 \longrightarrow CH_2OH.CH_2OH$$

On more vigorous oxidation (chromic acid, ozone) the chain is ruptured at the double bond, with the formation of aldehydes, ketones and acids.

It was shown by Harries in a series of investigations, that if olefins and other unsaturated substances, either in the pure state or in aqueous solution are treated with ozone, they form compounds containing a molecule of ozone attached to each double bond. On warming these explosive ozonides with water, they are decomposed into aldehydes or ketones, and hydrogen peroxide,

$$>C=C<+O_3 \longrightarrow >C\underset{O-\!-O}{\overset{O}{<}}C<$$

Ozonide.

$$+H_2O \longrightarrow >CO+>CO+H_2O_2$$

or they may yield a peroxide and an aldehyde, as illustrated below. This reaction offers a valuable method of determining the position of the double bond in an olefinic compound (see oleic acid).

$$(CH_3)_2C:CH.R+O_3 = (CH_3)_2C\underset{O-\!-O}{.O.}CH.R$$

$$\underset{\text{Ozonide}}{(CH_3)_2C\underset{O-\!-O}{.O.}CH.R} = \underset{\text{Peroxide}}{(CH_3)_2C:O:O}+\underset{\text{Aldehyde.}}{OCH.R}$$

The formulation of the ozonide given above is due to Staudinger and to Pummerer. In some cases an unstable *molozonide* may be temporarily

[1] Wieland and Sakellarios, *Ber.*, 1920, **53**, 201.

formed of the type $-CH(O-O:O)-CH-$; this alone gives rise to the polymerisation products sometimes isolated during ozonisation.[1]

Furthermore, the olefins are also capable of polymerisation, isobutylene, for example, being converted into di-isobutylene under the influence of dilute sulphuric acid, zinc chloride, or other reagents.

$$(CH_3)_2C:CH_2+(CH_3)_2C:CH_2 = (CH_3)_3C.CH:C(CH_3)_2$$

When heated under pressure they yield naphthenes, thus affording experimental evidence for the hypothesis of Engler that the naphthenes in petroleum are derived from ethylene homologues.[2]

Detection of the Ethylene Double Bond

Two of the foregoing reactions are of general use in testing for the presence of double bonds in unsaturated compounds, except in those containing certain ring systems to be described later.

(a) *Baeyer's Permanganate Test.*—According to Baeyer, alkaline permanganate is a general reagent for the recognition of unsaturated compounds. The test is carried out in aqueous solution by addition of a little sodium carbonate or bicarbonate and a drop of potassium permanganate. The colour of the latter rapidly disappears and a brown flocculent precipitate of a hydrated oxide of manganese forms. The reaction may also be performed in alcoholic solution, in which case a blank test should first be carried out with alcohol and permanganate alone. With compounds such as aldehydes, which already possess reducing properties, the reaction obviously gives no information as to the presence or absence of ethylene double bonds.

(b) *Addition of Bromine.*—Unsaturated compounds frequently absorb bromine with great ease, as is shown by shaking them with bromine water, when the colour disappears. (In very dilute aqueous solutions this yields bromohydrins, see p. 120.) It should be emphasised, however, that a number of substances are known, which, despite the presence of double bonds in the molecule, do not take up bromine.[3]

Formation of the Olefins

The following methods are of general application.

1. The dehydration of alcohols by means of concentrated sulphuric acid, phosphoric or oxalic acid, or zinc chloride.

$$\underset{\text{Ethyl alcohol}}{H_3C.CH_2.OH} = \underset{\text{Ethylene.}}{H_2C:CH_2}+H_2O$$

[1] See H. Staudinger, *Ber.*, 1925, **58**, 1088; R. Pummerer, *Ann.*, 1937, **529**, 33. [2] Engler and Routala, *Ber.*, 1909, **42**, 4613, 4620. Ipatiew, *Ber.*, 1911, **44**, 2978; 1913, **46**, 1748. [3] *Cf.* Nef, *Ann.*, 1897, **298**, 202. Bauer, *Ber.*, 1904, **37**, 3317.

Pure alumina has also been found to act as an energetic catalyst in splitting off the elements of water from alcohols, and olefins may be prepared by passing the vapour of an alcohol over alumina heated to 300°.[1]

Secondary and tertiary alcohols lose water more readily than the primary compounds.

Many tertiary alcohols pass into unsaturated hydrocarbons with extraordinary ease, sometimes spontaneously at the moment of their formation, or merely on distillation. For this reason olefins are frequently produced by the action of ketones on alkyl magnesium halides (see Grignard reaction), particularly when an excess of the latter is employed.[2]

When sulphuric acid is used the reaction is often complicated by polymerisation of the olefin under influence of the acid. Thus the formation of butylene, C_4H_8, is accompanied by the production of hydrocarbons of two and three times this molecular weight, viz., dibutylene, C_8H_{16}, and tributylene, $C_{12}H_{24}$.

2. The action of alcoholic sodium or potassium hydroxide on the alkyl halides, particularly the iodides.

$$C_nH_{2n+1}I+KOH = C_nH_{2n}+KI+H_2O$$

According to Sabatier and Mailhe,[3] finely divided metals (Ni, Cu, and Co), or anhydrous chlorides of divalent metals (Ni, Co, Cd, Fe, Pb, and Ba), also decompose alkyl halides into hydrogen halide and the corresponding olefin.

3. The electrolysis of concentrated aqueous solutions of the potassium salts of certain saturated dicarboxylic acids ; *e.g.* ethylene from potassium succinate.

$$\begin{matrix} H_2C\cdot CO_2K \\ | \\ H_2C\cdot CO_2K \end{matrix} + \begin{matrix} HO\cdot H \\ \\ HO\cdot H \end{matrix} = \begin{matrix} H_2C \\ \| \\ H_2C \end{matrix} + 2CO_2 + 2KOH + H_2$$

4. Olefins are often produced, together with paraffins, by the dry distillation of complex organic compounds, and hence ethylene is present in coal gas.

Ethylene, ethene, $H_2C{=}CH_2$, occurs to the extent of 4 to 5 per cent. in coal gas, and is usually prepared in the laboratory by heating one part of alcohol with four parts of concentrated sulphuric acid. In order to prevent frothing, sufficient sand may be added to bring the mixture to a pasty consistency. In this reaction ethyl-sulphuric acid is first formed, and on further heating breaks up into ethylene and sulphuric acid. The

$$C_2H_5OH+H_2SO_4 = C_2H_5SO_4H+H_2O\,;\; C_2H_5SO_4H = C_2H_4+H_2SO_4$$

gas is purified by bubbling through sodium hydroxide and concentrated sulphuric acid, in order to remove traces of carbon dioxide, sulphur dioxide, alcohol and ether. A less impure ethylene may be prepared by adding alcohol, drop by drop, to syrupy phosphoric acid heated to 220°.

For further methods of formation see above.

[1] Bouveault, *Bull. Soc. Chim.* (4), 3, 117. [2] Klages, *Ber.*, 1902, 35, 2633. Hell, *Ber.*, 1904, 37, 225, 230, 453, 1429, 4188. [3] See Sabatier and Mailhe, *J. C. S.*, 1908, A, i., 594, 713.

Properties.—Ethylene is a colourless gas possessing a faint ethereal smell; it is only slightly soluble in water, but more so in alcohol and ether. It burns with a luminous flame and forms an explosive mixture with oxygen. When led into bromine, rapid combination ensues with the formation of ethylene bromide, $C_2H_4Br_2$. Other properties of ethylene have been already described above. The oxidation of the gas by means of atmospheric oxygen has been examined by Willstätter and Bommer,[1] who found that formaldehyde was obtained in good yield. In view of

$$CH_2 : CH_2 + O_2 = 2CH_2O$$

the almost unlimited uses of formaldehyde, this reaction may yet prove of industrial importance.

Ethylene is now being utilised in an interesting manner in the fruit industry. When intended for transportation to considerable distances fruit is gathered and packed before it is fully ripe. On arrival at its final destination it is maintained for a few days in an atmosphere containing a small proportion of ethylene, which rapidly develops the colour and completes the ripening.

A few of the olefins, together with their boiling-points, are quoted in the following list. As may be seen, isomerism first occurs in the case of butene. Stereoisomerism [2] may also occur (see p. 48).

Propene, C_3H_6 = $H_3C.CH : CH_2$, b.p. $-40°$

Butenes, C_4H_8 =
1. $H_3C.CH_2.CH : CH_2$, ethyl-ethylene, b.p. $-5°$.
2. $H_3C.CH : CH.CH_3$, *plane*-sym. dimethyl ethylene,[2] b.p. $+1°$
   axially-sym. ,, b.p. $+2·5°$
3. $(H_3C)_2C : CH_2$, unsym. dimethyl-ethylene, b.p. $-6°$

Pentenes, C_5H_{10} =
1. $H_3C.CH_2.CH_2.CH : CH_2$, *n*-propyl-ethylene, or α-amylene, b.p. $+39°$
2. $H_3C.CH_2.CH : CH.CH_3$, sym. methyl-ethyl-ethylene, or β-amylene, b.p. $+36°$
3. $H_3C.CH_2 > C : CH_2$ (CH_3), unsym. methyl-ethyl-ethylene, or γ-amylene, b.p. $+31°$
4. $(H_3C)_2C : CH.CH_3$, trimethyl-ethylene, or β-isoamylene, b.p. $+36°$

Among the pentenes or amylenes, a mixture of which is obtained industrially by heating fusel oil with zinc chloride, trimethyl-ethylene or β-isoamylene is of special interest. It is employed under the name of *pental* as a narcotic of short duration, and also serves for the preparation of tertiary amyl alcohol.

2. Hydrocarbons, C_nH_{2n-2}.

Under the above general formula are classed two groups of hydrocarbons, the diolefins containing two ethylene bonds in the molecule, and the acetylenes containing a triple bond, named after acetylene, $HC{\equiv}CH$, the first member of the series.

Diolefins or Allylenes

For the *nomenclature* of these compounds compare p. 117.

In *properties and chemical behaviour* the diolefins show many resemblances to the olefins. They differ from the acetylenes in forming

[1] Willstätter, *Z. ang. Ch.*, 1919, **32**, 330. [2] For the stereoisomerism of the symmetrical dimethyl-ethylenes see Wislicenus, *Ann.* 1900, **313**, 207.

no copper or silver compounds. On the other hand, they give precipitates with a solution of mercuric chloride.

The manner in which hydrocarbons containing conjugated double bonds, C=C—C=C, unite with *two* monovalent atoms has already been discussed on pp. 21 and 22.

Formation.—Diolefins are obtained from the dibromo-substitution products of the saturated hydrocarbons by removing hydrogen bromide with alcoholic potash or quinoline; by heating the phosphates of diamines [1]; and by the *exhaustive methylation* of certain cyclic bases (p. 686). Since these compounds have recently been employed in the technical preparation of artificial caoutchouc, various synthetic methods have been devised for their manufacture, which are given in more detail under caoutchouc.

Allene, $H_2C:C:CH_2$, may be prepared by the electrolysis of potassium itaconate; also from tribromo-propane, $CH_2Br.CHBr.CH_2Br$, by removal of hydrogen bromide and bromine.

Butadiene, erythrene, 1 : 3-divinyl, $H_2C:CH.CH:CH_2$, is produced from erythritol by heating with formic acid, hence the name erythrene. A purer product may be obtained by the exhaustive methylation of N-methyl-pyrrolidine (see also Buna rubber).

1 : 3-Pentadiene, α-methyl-butadiene, piperylene, $H_2C:CH.CH:CH.CH_3$, is obtained in a similar manner from piperidine by exhaustive methylation.

Isoprene, β-methyl-butadiene (β-methyl-divinyl),

$$H_2C:C(CH_3).CH:CH_2$$

is the most important hydrocarbon of this series. As it is produced together with trimethylethylene and dipentene by the dry distillation of caoutchouc,[2] it is of importance in connection with the constitution of the latter. Isoprene may be prepared technically by various methods, *e.g.* from the isoamyl alcohol of fusel oil (p. 152) in the following stages:

$$(CH_3)_2CH.CH_2.CH_2OH \xrightarrow{HCl} (CH_3)_2CH.CH_2.CH_2Cl \xrightarrow{Cl_2} (CH_3)_2CCl.CH_2.CH_2Cl$$

Isoamyl alcohol — Isoamyl chloride — Dimethyl-trimethylene chloride.

$$\xrightarrow[\text{lime at } 470^\circ]{\text{over soda}} CH_2=\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}-CH=CH_2$$

Isoprene is a liquid, b.p. 37°; when heated to 300° under pressure it yields dipentene. In contact with sodium it polymerises to a rubber.

Isoprene is also of interest in connection with the chemistry of the carotenoids and the terpenes (p. 490).

Butadienes, in general, combine quantitatively with acrylic aldehyde, maleic anhydride and other compounds containing the group .CH : CH.CO. to form hydroaromatic derivatives (*Diels and Alder*). This furnishes an important synthetic method of preparing cyclic compounds (see p. 375).

The Acetylene Hydrocarbons

Nomenclature.—In addition to the details given on p. 117, it may be mentioned that compounds of this series are frequently named as

[1] Harries, *Ber.*, 1901, **34**, 300. [2] Wallach, *Ann.*, 1885, **227**, 295; Ipatiew, *J. Pr. Ch.* [2], 1897, **55**, 4.

substitution products of the first member, acetylene, CH : CH ; *e.g.* 3-butine or ethyl-acetylene, $C_2H_5.C : CH$.

Formation.—1. They can generally be prepared from the mono-halogen substitution products, or the dihalogen addition products, of the ethylene hydrocarbons, by heating with alcoholic potash, *e.g.* :

$$CH_2Br.CH_2Br + 2KOH = CH : CH + 2KBr + 2H_2O$$

An alcoholic solution of sodium or potassium ethoxide gives better yields, as there is then no tendency for the decomposition to stop at the intermediate stage of vinyl bromide.

2. Aldehydes and ketones also serve for the preparation of the acetylenes. With phosphorus pentachloride they are converted into dichloro-paraffins, which with potassium hydroxide yield acetylenes :

$$\underset{\text{Acetone}}{CH_3.CO.CH_3} \longrightarrow \underset{\text{2-Dichloro-propane}}{CH_3.CCl_2.CH_3} \longrightarrow \underset{\text{Methyl-acetylene.}}{CH_3.C : CH}$$

3. Acetylene and its homologues are also formed by the dry distillation of organic compounds and are therefore present in coal gas.

Properties and Chemical Behaviour.—In physical respects the acetylenes resemble the paraffins and olefins. The lower members of the series up to crotonylene, C_4H_6, are gases, then follow liquids and finally from $C_{16}H_{30}$ upwards they are solids.

The chemical behaviour of the acetylenes shows them to be strongly unsaturated. They unite readily with hydrogen, halogens and hydrogen halides, in two stages, each of which corresponds to the addition of one molecule of these substances. If two molecules of halogen acid are

$$CH : CH \xrightarrow{HBr} \underset{\text{Vinyl bromide}}{CH_2 : CHBr} \xrightarrow{HBr} \underset{\text{Ethylidene bromide}}{CH_3.CHBr_2}$$

taken up, both halogen atoms attach themselves to the same carbon atom. Under certain conditions *polymerisation* may take place, *e.g.* acetylene, C_2H_2, polymerises to form benzene, C_6H_6 ; and dimethyl-acetylene, C_4H_6, to hexamethyl-benzene, $C_{12}H_{18}$. This is an important method of passing from the aliphatic to the aromatic series, and the acetylene condensation is to be regarded as the main, though not the only, source of aromatic compounds in coal tar.[1]

A characteristic of acetylene and its monoalkyl-substitution products, R.C : CH, is the property of giving solid crystalline precipitates with ammoniacal solutions of silver and cuprous salts. In this reaction the hydrogen of the CH-group is substituted by metals to form acetylides of the type of copper acetylide, C_2Cu_2, which are explosive and regenerate the original hydrocarbon on warming with hydrochloric acid. By means of these metallic compounds acetylene may be purified and separated from other hydrocarbons. Besides these salts in which acetylene appears to function as an acid, additive compounds are known, *e.g.* CuCl, C_2H_2, produced by bringing acetylene into contact with the metallic salt.[2]

[1] Further pyrogenic acetylene condensations have been described by R. Meyer, see *Ber.*, 1912, 45, 1609. [2] Manchot, Withers and Oltrogge, *Ann.*, 1912, 387, 257.

ACETYLENE, ETHINE, CH≡CH.

Preparation.—Acetylene is readily prepared by dropping water on calcium carbide:

$$CaC_2+2H_2O = Ca(OH)_2+C_2H_2$$

The carbide is obtained industrially by heating quicklime with coke in an electric furnace, when the chief reaction takes place according to the equation

$$CaO+3C = CaC_2+CO$$

Certain other products are also formed from impurities in the lime, chiefly calcium phosphide from phosphates and ferrosilicon from iron and sand. For this reason the acetylene evolved from technical carbide is contaminated with ammonia, hydrogen sulphide and especially phosphine. Purification may be effected by washing with water to extract the ammonia, passing the gas over lime or hydrated iron ore to absorb hydrogen sulphide, and finally removing phosphine by means of bleaching powder, "heratol" (a mixture containing potassium bichromate and sulphuric acid), or other suitable oxidising mixtures.

The preparation of acetylene from calcium carbide in the laboratory is most conveniently carried out by placing the carbide in a dry flask, fitted with a separating funnel and a delivery tube, and allowing water to run in drop by drop from the funnel.

In addition to the methods of formation given above in the general section, acetylene is also produced by the following reactions.

It may be synthesised from its elements (Berthelot) by causing an electric arc to pass between two carbon electrodes in an atmosphere of hydrogen.

$$2C+2H = CH : CH$$

It is also formed by electrolysing solutions of the alkali salts of fumaric and maleic acids.

Acetylene is found among the gaseous distillation products of wood and coal, and is present in small amount (0·06 to 0·07 per cent. by volume) in coal gas. Furthermore it is formed during the incomplete combustion of many carbon compounds, and consequently the gases which escape when a bunsen burner strikes back also contain acetylene (0·75 to 0·80 per cent. by volume).

Properties.—Acetylene is a colourless poisonous gas of peculiar ethereal smell; it may be liquefied at 0° under a pressure of 26 atmospheres. At room temperature it dissolves in about its own volume of water, but it is considerably more soluble in organic liquids. Acetone, for example, at 15° takes up under ordinary pressure twenty-five times its own volume of acetylene. The gas is also adsorbed in great quantities[1] by colloidal or finely divided palladium. Acetylene is an endothermic compound (p. 103), and, as might be expected, is explosive, especially in the liquid state. Under the influence of a blow or an electric

[1] Paal and Hohenegger, *Ber.*, 1910, 43, 2684, 2692.

spark, and particularly when detonated by fulminate of mercury, acetylene decomposes spontaneously into its constituents with evolution of light and heat: $C_2H_2=2C+H_2$. Many disastrous explosions followed the first application of liquid acetylene to illumination on the large scale, as a result of which the manufacture and storage of the liquefied gas were forbidden by law. Subsequently it was discovered that when acetylene is dissolved in acetone, or admixed with other gases, especially ethylene or oil gas, it is insensitive to detonation, even under high pressures, and may then be used with safety.

Acetylene when ignited in the ordinary way burns with a luminous flame and the separation of a large amount of free carbon, but when burnt at a jet under certain pressure conditions (a head of 5 to 20 cm. of water) the flame is intensely bright and free from soot. When required as a source of illumination it is employed with specially designed jets which are so narrow as to be almost capillary. With air or oxygen the gas forms a strongly explosive mixture.

Under the influence of heat it undergoes polymerisation, three molecules combining to give one molecule of benzene, much tar being formed also. Since acetylene may be prepared from its elements this reaction furnishes a complete synthesis of benzene. On being passed over heated catalysts, *e.g.* clay at 650°, a tar is formed containing benzene, naphthalene and other aromatic hydrocarbons.

As mentioned above, both hydrogen atoms of acetylene are replaceable by metals, and the formation of the red copper compound, C_2Cu_2, may be utilised for the detection of very small amounts of the gas. In the dry state the acetylides of copper and silver are extraordinarily explosive. Under the catalytic influence of mercuric salts, acetylene combines with water to form acetaldehyde, which may readily be oxidised to give acetic acid. During recent years this process has been developed on the large scale, and adapted with great success to the manufacture of acetic acid.

Diacetylene, HC:C.C:CH, may be prepared from copper acetylide by oxidation with hot aqueous cupric chloride, and decomposing the copper derivative so obtained with dilute mineral acid. It boils at 10° under 760 mm. and polymerises with great ease.

II

Halogen Derivatives of the Hydrocarbons

The halogen derivatives of the hydrocarbons provide the most valuable starting material for the synthesis of organic compounds, and if only for this reason merit description in some detail. In addition it may be noted that several of them, such as chloroform, $CHCl_3$, and iodoform, CHI_3, are extensively used in medicine.

I.—HALOGEN DERIVATIVES OF THE PARAFFINS

Halogens normally function as monovalent elements, and a hydrocarbon such as methane would therefore be expected to yield four chlorine derivatives, CH_3Cl, CH_2Cl_2, $CHCl_3$ and CCl_4, as well as four bromine, iodine and fluorine compounds. Ethane, however, gives rise to nine instead of six chloro-derivatives, since in this case position isomerism is possible (*cf.* p. 19).

Methods of Formation.—1. The monohalogen derivatives or alkyl halides are most conveniently prepared from the corresponding alcohols, by replacing the hydroxyl group of the latter with halogen, either by the action of halogen acids,

$$\underset{\text{Ethyl alcohol}}{C_2H_5.OH} + HBr = \underset{\text{Ethyl bromide.}}{C_2H_5.Br} + H_2O$$

or of halogen compounds of phosphorus,

$$3C_2H_5.OH + PI_3 = \underset{\text{Ethyl iodide.}}{3C_2H_5.I} + H_3PO_3$$

In the latter case, at all events in introducing bromine and iodine, it is not always necessary to employ previously prepared phosphorus halide, this being usually formed during the course of the reaction. For example, ethyl iodide may be obtained by adding powdered iodine to a mixture of alcohol and red phosphorus, and warming to complete the reaction.

2. Alkyl halides are readily prepared by treating an aqueous solution of a metallic halide with dimethyl or diethyl sulphate. In this case only one of the alkyl groups takes part in the reaction, *e.g.*

$$\underset{\text{Dimethyl sulphate}}{SO_4(CH_3)_2} + KI = \underset{\text{Methyl iodide}}{CH_3I} + \underset{\text{Potassium methyl sulphate.}}{SO_4K(CH_3)}$$

3. Halogen derivatives are also obtained by the action of halogens on the paraffins (p. 109), but this is rarely used as a method of preparation since it usually leads to the formation of difficultly separable mixtures of isomerides and higher substitution products. Chlorine, for example, reacts with methane to yield CH_3Cl, CH_2Cl_2, $CHCl_3$ and CCl_4. The action of chlorine is particularly energetic in sunlight or in the presence of iodine, iron or antimony chloride (*chlorine carriers*); bromine reacts most easily when the reagents are warmed, or in the presence of aluminium bromide; iodine, however, has no action on the paraffins, unless in the presence of some substance such as mercuric oxide or iodic acid, which is able to remove the hydriodic acid formed.

4. As has been mentioned on pp. 119 and 126, the hydrocarbons of the olefin and acetylene series combine with halogens and hydrogen halides to form substitution products of the paraffins.

5. On treating aldehydes and ketones with phosphorus pentachloride the oxygen of the carbonyl group is replaced by halogen to yield dichloro-compounds,

$$\underset{\text{Acetaldehyde}}{CH_3.CH:O} + PCl_5 = \underset{\text{Ethylidene chloride.}}{CH_3.CHCl_2} + POCl_3$$

6. It has been shown that certain dihalogen derivatives may readily be obtained by the cleavage of cyclic amines with phosphorus pentachloride or bromide. N-Benzoyl piperidine, for example, on warming with phosphorus pentabromide, is converted smoothly into 1 : 5-dibromopentane [1] (see p. 685).

7. Alkyl chlorides may also be prepared from primary alcohols, by leading a mixture of hydrogen chloride and alcohol vapour at 370° to 450° over aluminium oxide as a catalyst.[2] In this way a mixture of the isomeric alkyl chlorides and the corresponding ethylene hydrocarbon is obtained. Propyl alcohol at 420° gives *sec*-propyl chloride, together with a small amount of propyl chloride.

The preparation of iodides from the chlorides and bromides is most conveniently effected by treating the latter with sodium iodide [3] in acetone solution.

Properties.—A few of these derivatives, such as methyl chloride, are gaseous under ordinary conditions, but the majority are colourless, sweet-smelling liquids. Those of high molecular weight are solid. The iodo-compounds are only colourless when freshly prepared ; they darken on standing, particularly under the influence of light, when decomposition occurs with the separation of free iodine. This may be minimised by the addition of some mercury, or a little finely divided (" molecular ") silver. Among similarly constituted compounds, the chlorides possess the lowest boiling-point ; the corresponding bromides boil approximately 25°, and the iodides 50°, higher than the chlorides. The iodides also possess the highest and the chlorides the lowest specific gravity, the figure sinking in each case as the hydrocarbon radical increases in magnitude. The halogen derivatives are not soluble in water, but dissolve readily in organic solvents such as alcohol, ether or carbon disulphide.

At low temperatures chlorine reacts with methyl or ethyl iodide to form an iodochloride, $CH_3.ICl_2$ or $C_2H_5.ICl_2$. Ethyl iodochloride decomposes in the neighbourhood of —36°.

With regard to the *chemical properties* of the alkyl halides, it should be noted that, in spite of certain resemblances to the metallic halides, they differ characteristically from the latter in their behaviour towards silver nitrate. As is well known, the metallic halides such as potassium iodide are ionised in solution, and react instantaneously with aqueous or alcoholic silver nitrate, all the halogen being precipitated as insoluble silver halide. The halogen substitution products of the hydrocarbons, on the other hand, are practically non-electrolytes, and either do not react with silver nitrate or the reaction sets in gradually. Pure chloroform, for example, may be shaken with aqueous silver nitrate without any separation of silver chloride, while ethyl iodide only very slowly yields a precipitate of silver iodide.

[1] J. v. Braun, *Ber.*, 1904, **37**, 2915, 3210. In a similar manner primary diamines may be converted into chlorinated amines and dichloro-derivatives, *Ber.*, 1905, **38**, 2340; 1909, **42**, 4541 ; 1911, **44**, 1464. [2] Sabatier and Mailhe, *C. r.*, 1919, **169**, 122. [3] H. Finkelstein, *Ber.*, 1910, **43**, 1528.

It must not be concluded from this behaviour with silver nitrate that the halogen is particularly firmly bound in the substituted aliphatic hydrocarbons, since by means of suitable reagents it is readily eliminated and replaced by hydroxyl, alkoxyl, amino or other groups. On this ease of reaction depends the extraordinary utility of the halogen derivatives, and especially the alkyl iodides, for organic synthesis. The latter are of great value in introducing alkyl groups into organic compounds, a process described in more detail in a later chapter.

In order to replace hydrogen in the hydroxyl group of an alcohol or acid by an alkyl radical, the sodium derivative of the alcohol or the silver salt of the acid may be heated with alkyl iodide. In some cases thallous salts of the acids give even better results.[1]

$$\underset{\text{Sodium ethoxide}}{C_2H_5.ONa} + C_2H_5I = \underset{\text{Diethyl ether.}}{C_2H_5.O.C_2H_5} + NaI$$

$$\underset{\text{Silver acetate}}{CH_3.COOAg} + C_2H_5I = \underset{\text{Ethyl acetate.}}{CH_3.COOC_2H_5} + AgI$$

In a similar manner it is possible to replace a hydrogen atom attached to nitrogen or carbon, *e.g.*

$$NH_3 + CH_3I = \underset{\text{Methylamine}}{CH_3.NH_2} + HI\,; \quad \underset{\text{Aniline}}{C_6H_5.NH_2} + 2CH_3I = \underset{\text{Dimethyl-aniline.}}{C_6H_5N(CH_3)_2} + 2HI$$

By means of the Würtz synthesis an iodine atom may be exchanged for an alkyl group,

$$\underset{\text{Ethyl iodide}}{C_2H_5I} + C_2H_5I + 2Na = \underset{\text{Butane.}}{C_2H_5.C_2H_5} + 2NaI$$

The preparation of unsaturated hydrocarbons from alkyl halides has already been referred to on pp. 123 and 126.

It will also be seen later that the alkyl halides have been extensively applied to the preparation of organo-metallic compounds, particularly those of zinc and magnesium (p. 136).

A final indication of the many-sided reactivity of the alkyl halides is given by their power of forming addition compounds with other substances, such as tertiary amines.

$$\underset{\text{Pyridine}}{C_5H_5N} + CH_3I = \underset{\text{Pyridine methiodide.}}{C_5H_5N\begin{matrix}\diagup I \\ \diagdown CH_3\end{matrix}}$$

Among the large number of substitution products of the paraffins known, the following are briefly described.

Methyl chloride, *chloro-methane*, CH_3Cl, is prepared by heating a mixture of methyl alcohol and hydrochloric acid with zinc chloride; also by heating trimethylamine hydrochloride, $N(CH_3)_3HCl$, obtained from the residual liquors in sugar manufacture, to 360°. It is a colourless, sweet-smelling gas which burns with a green-edged flame, and on being cooled condenses to a liquid, b.p. −23°. It comes on to the market in liquid form, and owing to the intense heat absorption resulting from its rapid evaporation, it is used for the production of low temperatures. **Ethyl chloride,** b.p. +12°, is for the same reason employed as a local anæsthetic.

[1] G. H. Christie and R. C. Menzies, *J. C. S.*, 1925, **127**, 2369; C. M. Fear and R. C. Menzies, *J. C. S.*, 1926, 937.

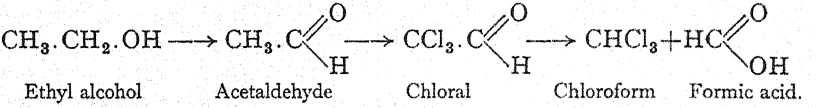
Methyl iodide, *iodo-methane*, CH_3I, may be prepared from methyl alcohol, iodine and red phosphorus. It is a liquid of pleasant ethereal odour, b.p. 44° and sp. gr. 2·27 at 25°. Under the influence of light it gradually darkens, owing to the separation of iodine.

Ethyl iodide, *iodo-ethane*, C_2H_5I, is prepared from ethyl alcohol, iodine and red phosphorus. Boiling-point 72·5° and sp. gr. 1·975.

Ethylene bromide, CH_2Br-CH_2Br, is obtained by passing ethylene gas into bromine. It is a colourless liquid of pleasant smell; b.p. 131°, m.p. 8°. It is much employed as a solvent and for synthetic purposes.

Chloroform, *trichloro-methane*, $CHCl_3$, is a chlorination product of methane or methyl chloride, and is formed by the action of bleaching powder on various organic substances such as alcohol, acetone, acetic acid and its salts, and tartaric acid.

The *method of preparation*, also used on the technical scale, is to distil aqueous alcohol with bleaching powder. It is supposed that the first step in this reaction is the oxidation of alcohol to aldehyde, which next undergoes substitution to trichloraldehyde (chloral), this being then hydrolysed by the lime present in the bleaching powder to formic acid and chloroform,



Ethyl alcohol — Acetaldehyde — Chloral — Chloroform — Formic acid.

Acetone may be used instead of alcohol in this preparation.

It is also possible to prepare chloroform by the electrolysis of a solution of potassium or calcium chloride in dilute aqueous alcohol or acetone.[1] The primary reaction consists in the formation of a hypochlorite and proceeds according to the equation :

$$\underset{\text{Acetone}}{CH_3.CO.CH_3} + 3HOCl = \underset{\text{Chloroform}}{CHCl_3} + \underset{\text{Acetic acid.}}{CH_3COOH} + 2H_2O$$

Chloroform prepared by any of the above methods is generally impure. It may be obtained in a very pure state, although at considerably greater expense, from chloral hydrate, which on heating with alkali decomposes into chloroform and the alkali salt of formic acid.

$$CCl_3.CHO + KOH = CHCl_3 + HCO_2K$$

Properties.—Chloroform is a colourless mobile liquid, b.p. 62° and sp. gr. 1·491 at 17°. It has a sickly sweet smell and a burning taste, dissolves readily in alcohol and ether, but only sparingly in water.

Inhalation of its vapour brings about loss of consciousness, and for this reason it is largely used as an anæsthetic in surgical operations. Chloroform was discovered almost simultaneously by Liebig and Soubeiran in 1831, but its anæsthetic properties remained unknown till their discovery in Edinburgh by Simpson in the year 1848.

Chloroform comparatively readily undergoes chemical changes. Under the influence of air and light it decomposes into chlorine, hydrochloric acid and carbonyl chloride, $COCl_2$. The specially purified

[1] J. Feyer, *Z. Elek.*, 1919, **25**, 115.

chloroform used for anæsthetic purposes is treated with a small amount —about 1 per cent.—of alcohol, and preserved in a dark bottle filled to the stopper, under which conditions the above decomposition is arrested. Chloroform reacts with chlorine to form carbon tetrachloride, CCl_4; when reduced with zinc and hydrochloric acid it yields methylene chloride, CH_2Cl_2. Concentrated nitric acid replaces the hydrogen atom with a nitro group, forming **chloropicrin,** CCl_3NO_2. When heated with aqueous or alcoholic potash, potassium formate is produced.

$$CHCl_3+4KOH = HCO_2K+3KCl+2H_2O$$
Potassium formate.

Chloroform may be tested for by warming with a primary amine (usually aniline) and alcoholic potash. An isonitrile is thus formed possessing a characteristically unpleasant odour. This reaction may be employed for the detection of primary amines as well as of chloroform.

$$C_6H_5NH_2+CHCl_3+3KOH = C_6H_5NC+3KCl+3H_2O$$
Aniline — Phenyl carbamine.

Tests for Impurity.—Chloroform for anæsthetic purposes must be of the highest grade of purity. When shaken with water, the aqueous layer should not become acid, nor give any cloudiness with silver nitrate.

Bromoform, *tribromomethane*, $CHBr_3$, is prepared in a similar manner to chloroform by the action of bromine on alcohol or acetone, and is a liquid, boiling at 151°.

Iodoform, *triiodomethane*, CHI_3, is produced by the action of iodine and caustic alkali on alcohol, acetaldehyde or acetone. This is known as the *haloform reaction*[1]; in general it is given by any compound containing the group $CH_3.CO$ linked to carbon or hydrogen, or any group such as $CH_3.CH(OH)$ which may be converted into $CH_3.CO$ by the oxidising action of the reagent.

Technically it is prepared by warming a mixture of iodine, alcohol, and caustic potash or potassium carbonate.

$$C_2H_5OH+8I+6KOH = CHI_3+HCO_2K+5KI+5H_2O$$
Potassium formate.

Acetone may also be used in place of alcohol as starting material.

A modern method of preparation is by the electrolysis of an aqueous alcoholic solution of potassium iodide and carbonate.[2]

Properties.—Iodoform crystallises in yellow hexagonal plates of characteristic smell; it melts at 119°, readily sublimes and is volatile with steam. It is insoluble in water, but soluble in alcohol and ether. On treatment with an alcoholic solution of potassium ethoxide, or on reduction with hydriodic acid and phosphorus, methylene iodide, CH_2I_2, is formed. Iodoform is extensively used in surgery as an antiseptic.

Carbon tetrachloride, *tetrachloromethane*, CCl_4, is obtained as a colourless liquid, b.p. 76°, by the action of chlorine on chloroform or

[1] For an excellent survey of the haloform reaction see R. C. Fuson and B. A. Bull, *Chem. Rev.*, 1934, 273. [2] *C.*, 1897, **II**, 695; 1898, **I**, 31; 1900, **II**, 719; *J. Phys. Ch.*, 1903, **7**, 84. Feyer, *Z. Elek.*, 1919, **25**, 115.

carbon bisulphide. It is largely used as a solvent. Technically, the chlorination of carbon bisulphide is effected with the aid of aluminium chloride or manganese chloride as catalyst.

A series of chlorinated compounds, all prepared from acetylene, have recently come into use as valuable non-inflammable solvents. These polyhalogen derivatives are far less reactive than the mono-halogenated compounds.

Acetylene tetrachloride, *tetrachloroethane*, $CHCl_2.CHCl_2$, is obtained by the addition of chlorine to acetylene in the presence of infusorial earth (*kieselguhr*) or other diluent, in the absence of which combination occurs explosively. It is a heavy non-inflammable liquid, b.p. 147°, sp. gr. 1·601 at 15°, which is used technically under the name of *Westron* as a solvent for cellulose acetate varnishes, for rubber and fats, and also as an insecticide.

When the vapour of acetylene tetrachloride is passed over a catalyst ($BaCl_2$ or ThO_2) at 350°, one molecule of HCl is lost and **trichloro-ethylene,** *Westrosol*, $CCl_2 : CHCl$, b.p. 87°, sp. gr. 1·471 at 15°, is formed. This is used industrially for the extraction of oils from seeds, and for dry cleaning. The halogen in trichloro-ethylene is very stable, and is not appreciably attacked by the common metals, even in the presence of moisture.

Acetylene dichloride, *dichloro-ethylene*, $CHCl : CHCl$, sp. gr. 1·278 at 15°, is prepared industrially as a mixture of two isomerides (b.p. 48° and 60°) by treating *Westron* with zinc in the presence of water. It is

$$CHCl_2.CHCl_2 + Zn = CHCl{:}CHCl + ZnCl_2$$

used for extractions in place of ether or light petroleum. The hot vapours may be ignited but the flame rapidly extinguishes itself.

Carbon hexachloride, *hexachloroethane*, C_2Cl_6, is a solid, melting at 187°.

II.—HALOGEN DERIVATIVES OF THE UNSATURATED HYDROCARBONS

Only in exceptional cases are these compounds produced directly by the action of halogens on unsaturated hydrocarbons, since the first action of the halogen is generally to form an addition compound and not to substitute.[1] We can, however, obtain the desired derivatives from these addition products by the partial removal of hydrogen halide with alcoholic potash, for example :

$$H_2C : CH_2 \xrightarrow{+Br_2} H_2CBr.CH_2Br \xrightarrow{-HBr} \underset{\text{Vinyl bromide.}}{H_2C : CHBr};$$

$$\underset{\text{Sym. tetrabromoethane}}{HCBr_2.CHBr_2} \xrightarrow{-HBr} \underset{\text{Tribromoethylene}}{HCBr : CBr_2} \xrightarrow{-HBr} \underset{\text{Dibromoacetylene.}}{CBr : CBr}$$

[1] *Cf.* Biltz and Küpper, *Ber.*, 1904, **37**, 4412, for the substitution of hydrogen by iodine, by use of iodine and sodium hypoiodite. [2] *C.*, 1903, **II**, 102.

The halogen derivatives of the olefins, in which halogen is united to a doubly bound carbon atom, differ markedly from the corresponding paraffin derivatives in that the halogen is in general not replaceable by other radicals such as hydroxyl. Like the olefins themselves, they readily combine with halogens and halogen acids, and exist in geometrically isomeric forms (p. 48).

Those halogen derivatives of the olefins in which, as in allyl iodide, $H_2C : CH.CH_2I$, the halogen is attached to a singly bound carbon atom, resemble the paraffin compounds in the reactivity of the halogen.

The halogen derivatives of the acetylenes, like other acetylene compounds, are very unstable and readily undergo explosive decomposition; they also show a strong tendency to polymerise.

Vinyl chloride,[1] monochloroethylene, $CH_2 : CHCl$, is gaseous at ordinary temperatures. Vinyl bromide boils at 16°.

Allyl iodide, $H_2C : CH.CH_2I$, may be obtained from allyl alcohol, or more simply from glycerol, by heating with hydriodic acid, or with iodine and phosphorus. It is a colourless liquid, b.p. 102°, which smells of leeks, and occurs in the combined state in mustard oil and oil of garlic. It is frequently employed in syntheses for the introduction of the allyl group.

Tetraiodo-ethylene, $CI_2 : CI_2$, is obtained in lemon yellow crystals, m.p. 187°, when calcium carbide is added to a solution of iodine in potassium iodide at 0°. It is odourless and possesses antiseptic properties.

$$C_2Ca+6I = C_2I_4+CaI_2$$

Diiodo-acetylene, $CI : CI$, is also formed during the above reaction. It crystallises in colourless needles, m.p. 78°, and is very volatile. The vapour strongly attacks the mucous membranes.

$$C_2Ca+4I = C_2I_2+CaI_2$$

For other *chloro-derivatives of acetylene* see previous page.

III

Organo-metallic Compounds

The organo-metallic compounds are usually prepared by the action of metals, such as zinc, magnesium or mercury, on the alkyl iodides, and owing to their reactivity are frequently employed in synthetic reactions. The zinc and magnesium compounds are the most important of this class, and it is only recently that the simpler derivatives of the alkali metals have been carefully studied.

Sodium alkyls, *e.g.* sodium methyl, $NaCH_3$, are obtained by the action of sodium on the corresponding mercury alkyls.[2] In the pure state they form colourless amorphous solids which are completely insoluble

[1] The radical $H_2C=CH-$ is known as vinyl. [2] W. Schlenk and Holtz, *Ber.*, 1917, **50**, 262.

in indifferent solvents, and when heated decompose without melting. They are extremely sensitive towards oxygen, moisture and carbon dioxide, are inflammable in air and very reactive.[1]

Zinc alkyls were discovered in 1849 by Frankland. They are obtained by the action of excess of zinc on alkyl iodides. The reaction is facilitated by using zinc in the form of the zinc-copper couple and by addition of ethyl acetate. Zinc alkyl iodides are first formed which decompose into zinc alkyls and zinc iodide on distillation.

$$C_2H_5I+Zn = C_2H_5ZnI\,;\ 2C_2H_5ZnI = Zn(C_2H_5)_2+ZnI_2$$

The zinc alkyls are colourless, unpleasant smelling liquids which boil without decomposition at relatively low temperatures in an atmosphere of carbon dioxide. They are spontaneously inflammable in air, and produce painful burns in contact with the skin. Consequently they must be handled with caution. Nevertheless they were examined in detail by Frankland, who showed that they could be used for the synthesis of a variety of compounds, including alcohols and ketones (p. 177).

Zinc methyl, $Zn(CH_3)_2$, b.p. 46°; *zinc ethyl*, $Zn(C_2H_5)_2$, b.p. 118°; *zinc propyl*, $Zn(C_3H_7)_2$, b.p. 146°.

With water they decompose to form paraffins and zinc hydroxide.

$$Zn(CH_3)_2+2H_2O = Zn(OH)_2+2CH_4$$

Paraffins are also produced on heating zinc alkyls to a high temperature with alkyl iodides.

$$Zn(CH_3)_2+2CH_3I = ZnI_2+2H_3C.CH_3$$

Frankland's work on the metallic alkyls was extended to derivatives of other metals, *e.g.* trimethyl arsine, $As(CH_3)_3$ and trimethyl stibine, $Sb(CH_3)_3$, which first led to the belief that each element had a definite combining power and so laid the foundation of the modern theory of valency.

Organo-magnesium Compounds.—It is only in modern times, with the discovery that free magnesium alkyls could be replaced by the readily soluble compounds of the type RMgI, that the organo-magnesium derivatives have been used with such great success in synthesis.

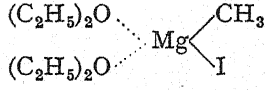
It was shown by Grignard,[2] in a series of publications, that magnesium in the presence of dry ether interacts with numerous organic halogen compounds, particularly alkyl iodides and bromides, to form compounds of the above type which remain dissolved in the ether. At the same time it was found that the magnesium alkyl halides did not require to be isolated for synthetic purposes, but could be used directly in ethereal solution. They are solids and are not spontaneously inflammable in air.

Reactions between metallic magnesium and alkyl or aryl halides in ethereal solution are known as *Grignard reactions*, and compounds of the general formula R.Mg.Hal as *organo-magnesium halides*.

[1] Schorigin, *Ber.*, 1908, **41**, 2717; 1910, **43**, 1931. Schlubach, *Ber.*, 1919, **52**, 1910.
[2] Grignard, *Annales de l'Université de Lyon*, 1901, pp. 1 to 116.

It was shown later by Tschelinzeff [1] that the formation of these compounds also takes place slowly in other solvents such as benzene, toluene and xylene, in the presence of a trace of ether. The amount of organo-magnesium halide formed is out of all proportion to the quantity of ether employed, from which it was concluded that in the Grignard reaction the ether plays the part of a *catalyst*. [2]

Tschelinzeff also found that other substances could act as catalysts. The formation of organo-magnesium compounds takes place in solvents such as benzene, toluene, xylene and petroleum ether, when a few drops of a tertiary amine (*e.g.* dimethyl-aniline) are added. In this case the magnesium compound is thrown out of solution as a white flocculent precipitate corresponding to the formula R.Mg.Hal. This is sometimes of practical as well as theoretical importance, since the catalytic influence of the tertiary amine is in some cases far more energetic than that of ether, and the reaction often takes place more rapidly and with as good a yield as by the Grignard method. Nevertheless, Grignard's method of preparing the compounds in dry ether solution is generally more convenient. If desired, the magnesium alkyl halides may be isolated in combination with two molecules of ether, *e.g.* CH_3MgI, $2(C_2H_5)_2O$. According to Meisenheimer these compounds are regarded as complexes of magnesium in which the metal occurs as the central atom with a co-ordination number 4.



By reason of their extraordinary reactivity the organo-magnesium compounds aroused great interest, and the original investigations of Grignard were immediately followed by those of a number of other workers. It was soon apparent that for synthetic purposes magnesium compounds of the type R.Mg.Hal were more conveniently manipulated, gave better yields, and were of more general utility than the zinc alkyls. Already they have attained a position in synthetic chemistry unrivalled by that of any other class of compound. A recent development is the discovery by Schlenk [3] that the organo-magnesium halide exists in solution in equilibrium with magnesium halide and the compound of type MgR_2.

$$2CH_3.Mg.I \rightleftarrows Mg(CH_3)_2 + MgI_2$$

It therefore appears probable that some of the activity of the Grignard reagent is associated with the presence of magnesium dialkyl or diaryl.

With the aid of the Grignard reaction it is possible to synthesise hydrocarbons, primary, secondary and tertiary alcohols, ethers, ketones, aldehydes, carboxy- and thio-acids, phenols and thiophenols, and a variety of nitrogen compounds, as well as other alkyl metallic derivatives.

[1] Tschelinzeff, *Ber.*, 1904, **37**, 4534. [2] A chemical process, the velocity of which depends greatly upon the presence of some particular substance which is not itself used up in the chemical change, is termed a *catalytic reaction*, the substance in question being known as a *catalyst*.
[3] W. Schlenk and W. Schlenk, jun., *Ber.*, 1929, **62**, 920.

For examples of the use of alkyl magnesium halides in synthetic work, see alcohols, p. 144, and in the index under *Grignard reaction*.

In addition to the above compounds, alkyl derivatives of many other metals, including mercury, lead, tin [1] and lithium, have also been prepared. The mercury compounds HgR_2 are extremely poisonous liquids.

The **lead alkyls,** *e.g. lead tetramethyl*, $Pb(CH_3)_4$, b.p. 110°, possess a special interest as illustrating the tetravalency of lead. They are most conveniently obtained by acting on alkyl magnesium halides with lead chloride.

$$2PbCl_2+4CH_3MgI = Pb+Pb(CH_3)_4+4MgICl$$

On being heated they decompose, liberating free alkyls which rapidly polymerise. **Lead tetraethyl** is prepared industrially from sodium-lead alloy and ethyl chloride. It is added in small proportion to petrol as an " anti-knock " agent (*Ethyl petrol*).

Unsaturated organic compounds of lead, in which the lead atom appears to be united to carbon groups by less than four valency bonds, are formed by the action of alkyl halides on lead sodium amalgam, by the electrolytic reduction of ketones at lead cathodes,[2] and by the action of certain alkyl magnesium halides on lead chloride.[3] The most interesting of these compounds are the lead triaryls,[4] $PbAr_3$, which correspond to triphenylmethyl (p. 520).

Organic Derivatives of Arsenic.—These were discovered as early as 1760, when Cadet observed the formation of a " fuming arsenical liquid " on heating potassium acetate with arsenic trioxide. But it was not until this reaction was investigated in detail by Bunsen that the structure of the cacodyl oxide thus produced was established. Bunsen proved that the cacodyl radical, $(CH_3)_2As$, occurred unchanged throughout a series of derivatives and so provided further support for the theory of radicals.

Cacodyl oxide, $[(CH_3)_2As]_2O$, b.p. 150°, is obtained by distilling a mixture of potassium acetate and arsenic trioxide. The liquid is insoluble

$$As_2O_3+4CH_3.COOK = [(CH_3)_2As]_2O+2CO_2+2K_2CO_3$$

in water, possesses a nauseous odour (cacodyl=stinking) and its vapour is unbearably irritating to the mucous membrane. As prepared by the above method the oxide is contaminated with *tetramethyl-diarsine* (cacodyl), forming a mixture which fumes in air and may undergo spontaneous combustion. On distillation with hydrochloric acid the crude oxide is converted into *cacodyl chloride*, from which the pure oxide may be regenerated by treatment with alkali. **Cacodyl chloride,** *dimethyl-arsine chloride*, $(CH_3)_2AsCl$, boils at 100° and has an even more stupefying odour than the oxide. It is spontaneously inflammable in air. When

$$(CH_3)_2As.O.As(CH_3)_2+2HCl = 2(CH_3)_2As.Cl+H_2O$$

[1] For alkyl compounds of tin see Pope and Peachey, *Proc. Chem. Soc.*, 1903, **19**, 290, and P. Pfeiffer, *Ber.*, 1911, **44**, 1269; for organic silicon compounds see G. Martin, *Ber.*, 1913, **46**, 3289. [2] Tafel, *Ber.*, 1911, **44**, 323. [3] Grüttner and Krause, *Ber.*, 1916, **49**, 1416. [4] Krause and Schmitz, *Ber.*, 1919, **52**, 2165; Krause and Reiszaus, *Ber.*, 1922, **55**, 888.

reduced with zinc or mercury in an atmosphere of CO_2 it yields **tetramethyl-diarsine,** *cacodyl*, $(CH_3)_2As.As(CH_3)_2$. This is also a spontaneously inflammable liquid, which boils at 170° and possesses the same unpleasant physiological properties as the chloride and oxide. As Bunsen first showed, cacodyl behaves as an " organic element," uniting with oxygen, chlorine and sulphur, etc., to form the corresponding derivatives.

Cacodyl oxide may be oxidised slowly in air or more rapidly by use of mercuric oxide to give **cacodylic acid,** $(CH_3)_2As\begin{matrix}=O\\ -OH\end{matrix}$. The latter is a weak acid, which melts at 200° and is odourless. Closely related to this compound is **methyl arsinic acid,** obtained as its disodium salt by direct methylation of sodium arsenite with dimethyl sulphate at 85°. Both of the above acids have been utilised medicinally in the form of

$$Na_3AsO_3 \longrightarrow CH_3.AsO_3Na_2.$$

their sodium salts for the treatment of skin and other diseases. Various aromatic arsenic derivatives employed for the same purpose are described later.

Methyl dichloroarsine,[1] CH_3AsCl_2, has been used in warfare as a poison gas. Disodium methyl-arsenite, prepared as already indicated by the methylation of sodium arsenite, is treated with sulphurous acid to convert it into methyl-arsine oxide, which is then brought into reaction with gaseous hydrochloric acid to give methyl dichloroarsine. It may be separated from admixed methyl alcohol and hydrochloric acid by fractional distillation, and boils at 130° to 132°.

IV

The Alcohols

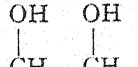
Classification.—The alcohols may be derived theoretically from the hydrocarbons by replacing a hydrogen atom of the latter by a hydroxyl group. Generally speaking, therefore, they may be regarded as alkyl hydroxides (in which the alkyl radical may be saturated or unsaturated) with a constitution resembling that of the metallic hydroxides. At the same time it should be emphasised that in their typical properties alcohols and inorganic bases show considerable differences. The inorganic bases are electrolytes and alkaline in reaction, the alcohols are non-electrolytes and neutral. As will be seen later, both alcohols and bases react with acids with elimination of water.

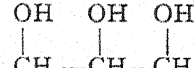
Corresponding to mono- and polyacid bases we have mono- and polyhydric alcohols. If one hydrogen in a hydrocarbon is replaced by

[1] Uhlinger and Cook, *J. Ind. and Eng. Ch.*, 1919, **II**, 105.

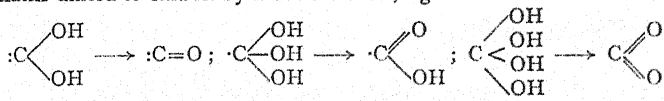
OH we obtain a monohydric alcohol; if two hydrogens attached to *different* carbon atoms are exchanged for hydroxyls we obtain a dihydric alcohol, and so on. Alcohols are known containing three, four, five, six and more hydroxyl groups.

Examples: $CH_3.OH$
Monohydric alcohol
Methyl alcohol


Dihydric alcohol
Ethylene glycol


Trihydric alcohol
Glycerol.

If two or more hydroxyl groups are attached to the same carbon atom, they represent an unstable formation. In such cases, with few exceptions, water is eliminated and oxygen remains united to carbon by a double bond, *e.g.*



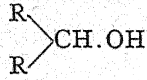
According as the hydroxyl group is linked to a primary, secondary or tertiary carbon atom (p. 106) we speak of a primary, secondary or tertiary alcohol.

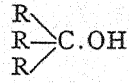
Primary alcohols therefore contain the group $—CH_2.OH$, in which the free bond is linked to carbon. On oxidation [1] they are first converted into aldehydes, the group $—CH_2.OH$ being transformed into $—CH:O$. The latter on further oxidation form acids, containing the group —COOH and having the same number of carbon atoms as the original alcohol.

Secondary alcohols contain the group $>CH.OH$. These on oxidation are converted into ketones of the same number of carbon atoms, the group $>CH.OH$ being oxidised to $>C:O$. On further oxidation the molecule breaks down, yielding acids containing a smaller number of carbon atoms.

Tertiary alcohols contain the group . They break down on oxidation, giving ketones and acids, each containing fewer carbon atoms than the original alcohol.

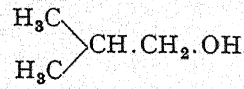
$R.CH_2.OH$
Primary alcohol


Secondary alcohol


Tertiary alcohol.

Isomerism and Nomenclature.—As in the case of hydrocarbons, we may have structural isomerism among alcohols due to differences in the linking of the carbon chains (I and II), the primary alcohol which corresponds to the normally constituted hydrocarbon being termed a normal alcohol.

I. $CH_3.CH_2.CH_2.CH_2.OH$
Normal primary butyl alcohol
or propyl carbinol

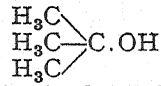
II. 
Isobutyl alcohol
or isopropyl carbinol.

[1] For the mechanism of the process of oxidation see Wieland, *Ber.*, 1912, **45**, 488, 2606; *Ber.*, 1913, **46**, 3327. Bone, *J. C. S.*, 1933, 1604. Compare also the slow combustion of hydrocarbons, p. 110.

Isomerism may also be occasioned by the different position of the hydroxyl in the molecule (I and III), or both these variations may occur together (I and IV).

III. $CH_3.CH_2.CHOH.CH_3$

Normal secondary butyl alcohol or methyl ethyl carbinol

IV. 

Tertiary butyl alcohol or trimethyl carbinol.

A convenient nomenclature for such isomerides is obtained by considering them as substitution products of methyl alcohol, CH_3OH, by naming the latter carbinol and the higher alcohols as substituted carbinols (see above formulæ).

According to the Geneva nomenclature, the names of the alcohols are obtained from those of the hydrocarbons from which they are derived by replacing the final -e by -ol. Polyhydric alcohols are designated as diols, triols and so on.

$CH_3.OH$
Methyl alcohol, Methanol

$HO.CH_2.CH_2.OH$
Glycol or ethandiol

$HO.CH_2.CHOH.CH_2.OH$
Glycerol, propantriol.

$CH_2:CH.CH_2OH$
Allyl alcohol, 1-propene-3-ol.

If a hydroxyl group is attached to a side chain, the name of the latter takes the termination -ol.

MONOHYDRIC ALCOHOLS

As already mentioned, these may be derived from saturated or unsaturated hydrocarbons. The unsaturated alcohols differ from the saturated in their additive properties only, resembling them in all typical reactions, so that they are conveniently treated together.

The *physical properties* of the monohydric alcohols vary from member to member, just as is the case with any other homologous series. The first members are mobile liquids—gaseous alcohols being unknown—after which follow those of oily consistency, and from dodecyl alcohol, $C_{12}H_{25}OH$, onwards they are wax-like solids. Solubility in water diminishes with increase in molecular weight, the first members of the series being miscible in all proportions, whereas the higher alcohols are quite insoluble. The lower compounds possess a characteristic alcoholic smell and taste, the intermediate members have an unpleasant smell, and those of high complexity are tasteless and odourless. For alcohols of similar structure the boiling-point rises regularly with increase of molecular weight. Each difference of CH_2 corresponds to a rise of approximately 20°. The highest members (above C_{16}) decompose on distillation, unless this is conducted under diminished pressure. Primary alcohols boil higher than the isomeric secondary, and these again higher than the corresponding tertiary compounds. The specific gravity is in all cases less than unity.

It must be emphasised that the *chemical behaviour* of the hydrogen

atom in the hydroxyl group OH, a group common to all alcohols, is very different from that of the hydrogen atoms in the alkyl radical, being directly replaceable by metals such as sodium and potassium, with evolution of hydrogen and formation of *alcoholates* or *alkoxides*.

$$\underset{\text{Ethyl alcohol}}{C_2H_5.OH}+Na = \underset{\text{Sodium ethoxide.}}{C_2H_5.ONa}+H$$

Alcohols react with acids to form **esters**, *e.g.* ethyl nitrate.

$$\underset{\text{Ethyl alcohol}}{C_2H_5.OH}+HNO_3 = \underset{\text{Ethyl nitrate.}}{C_2H_5.O.NO_2}+H_2O$$

$$NaOH+HNO_3 = NaNO_3+H_2O$$

As already indicated, we may compare esters to the salts of inorganic chemistry, and the formation of esters from alcohols to that of salts from bases. Nevertheless, these processes differ distinctly in their mechanism. The formation of a salt is an ionic reaction and proceeds instantaneously; whereas ester formation from acid and unionised alcohol progresses slowly.[1]

Alcohols also resemble the hydroxide bases in combining, with elimination of water, to produce anhydrides corresponding to the inorganic oxides. These anhydrides are termed **ethers**:

$$2C_2H_5OH-H_2O = \underset{\text{Diethyl ether}}{C_2H_5.O.C_2H_5} \qquad 2LiOH-H_2O = Li_2O$$

The dehydration of alcohols may also give rise to olefins (p. 122), $C_2H_5OH \longrightarrow CH_2 : CH_2$. This occurs very readily in the case of tertiary alcohols.

On treatment with phosphorus halides the hydroxyl group of the alcohols is replaced by halogen, forming alkyl halides (p. 129).

Methyl magnesium iodide interacts with alcohols, and in general with any hydroxy compound, with liberation of one molecule of methane for each hydroxyl group present:

$$CH_3.MgI+R.OH = CH_4+R.OMgI$$

The methane so formed is easily recognised and can be quantitatively estimated. This reaction may be used for determining the number of hydroxyl groups in a compound.[2]

The characteristic behaviour on oxidation, which serves for the identification of primary, secondary and tertiary alcohols, has already been discussed in the beginning of this section.

Primary, secondary and tertiary alcohols differ also in their behaviour towards hot reduced copper, as was shown by Sabatier and Senderens.[3] On being led over reduced copper at 300° primary alcohols break up

[1] The rate of esterification of alcohols varies with their constitution and diminishes progressively as we pass from primary to secondary and from the latter to tertiary alcohols. *Cf.* Menschutkin, *Ann.*, 1879, **197**, 193; Michael, *Ber.*, 1909, **42**, 3157. [2] Zerewitinoff, *Ber.*, 1907, **40**, 2023. [3] Sabatier and Senderens, *C.*, 1905, **I**, 1002. For many years the decomposition of alcohols by metallic oxides has been the subject of numerous investigations. *Cf.* Mailhe, *Ch. Zeit.*, 1909, **33**, 18, 29.

into aldehydes and hydrogen, secondary alcohols yield ketones and hydrogen, and tertiary compounds decompose into water and olefins.

$$\underset{\text{Ethyl alcohol}}{CH_3.CH_2.OH} = \underset{\text{Acetaldehyde.}}{CH_3.CH:O} + H_2$$

$$\underset{\text{2-Propanol}}{CH_3.CHOH.CH_3} = \underset{\text{Acetone.}}{CH_3.CO.CH_3} + H_2$$

$$\underset{\text{2-Methyl-2-propanol}}{\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C(OH).CH_3} = \underset{\text{2-Methyl-propene.}}{\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C:CH_2} + H_2O$$

With halogens the alcohols are not substituted but oxidised.

Calcium chloride unites with alcohols to form double compounds which are decomposed by water, consequently it is not a suitable drying agent for alcohols.

Methods of Formation.—(*a*) Alcohols may be obtained from alkyl halides by exchanging the halogen atom for hydroxyl, either by treating them with moist freshly prepared silver oxide at the ordinary temperature or with gentle warming, or by heating them with lead oxide and water.

$$C_2H_5I + AgOH = C_2H_5OH + AgI$$

Alkalis bring about the same change, but tend to remove hydrogen halide, with the simultaneous formation of olefins. Tertiary halides readily undergo conversion into alcohol in contact with water alone.

(*b*) Alcohols occurring in nature are found almost exclusively in combination with organic acids in the form of esters, *e.g.* in certain plant oils, and in fats and waxes. They may be prepared from these sources by heating with aqueous mineral acids or alkalis, or by the action of superheated steam. This process is termed **hydrolysis** (see p. 156).

(*c*) A method of great industrial importance is the formation of alcohols by the fermentation of carbohydrates. In this manner ethyl alcohol may be prepared from glucose by fermentation with yeast.

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \longrightarrow \underset{\text{Alcohol.}}{2C_2H_5OH} + 2CO_2$$

Similarly *n*-primary butyl alcohol is manufactured from starch by fermentation with *B. Clostridium acetobutylicum.*

(*d*) By the action of nitrous acid on primary amines the group NH_2 may be replaced by OH, and a primary alcohol formed. In some cases

$$\underset{\text{Ethylamine}}{C_2H_5.NH_2} + HNO_2 = \underset{\text{Ethyl alcohol.}}{C_2H_5.OH} + N_2 + H_2O$$

rearrangement occurs. Thus *n*-propylamine, $CH_3.CH_2.CH_2.NH_2$, yields with nitrous acid a mixture of *n*-propyl alcohol, $CH_3.CH_2.CH_2.OH$, and isopropyl alcohol, $(CH_3)_2CH.OH$.

(*e*) A general method of preparing primary alcohols consists in the reduction of aldehydes, *e.g.* by use of sodium amalgam and very dilute mineral acid, or of zinc dust and acetic acid. In a similar manner ketones yield secondary alcohols.

$$\underset{\text{Acetaldehyde}}{CH_3.CH:O} + 2H = \underset{\text{Ethanol}}{CH_3.CH_2OH}; \quad \underset{\text{Acetone}}{CH_3.CO.CH_3} + 2H = \underset{\text{Isopropyl alcohol.}}{CH_3.CH(OH).CH_3}$$

The reduction may be effected rapidly and in high yield by use of hydrogen in the presence of finely divided platinum or palladium at ordinary temperatures in a hydrogenation apparatus.

It is also practicable to reduce ketones, and more especially aldehydes, by a phytochemical method using living yeast.[1] The biological nature of the reaction is indicated in those cases where an asymmetric carbon atom is involved by isolation of the alcohols in an optically active although not optically pure state.

Esters, acid chlorides and acid anhydrides can be reduced to alcohols by use of sodium amalgam or sodium.

(*f*) Numerous syntheses of alcohols have been carried out by use of organomagnesium halides of the type $C_nH_{2n+1}MgX$ (where X=Cl, Br or I). These reagents unite with oxygen and with compounds containing a carbonyl group (such as aldehydes, ketones and esters) to form addition products which yield alcohols on being decomposed with ice and dilute acids.

Primary alcohols are obtained by passing dry oxygen into an ethereal solution of the reagent prepared from a primary halide, or by treating

$$R.CH_2.Mg.Cl + O \longrightarrow R.CH_2.O.MgCl \xrightarrow{HCl} R.CH_2.OH + MgCl_2$$

the reagent with formaldehyde.[2]

$$H.CH:O + R.MgCl \longrightarrow H.CH\begin{matrix}\diagup OMgCl \\ \diagdown R\end{matrix} \xrightarrow{HCl} R.CH_2OH + MgCl_2$$

Secondary alcohols result from the interaction of alkyl magnesium halides with aldehydes or with formic esters, whereas *tertiary alcohols* are obtained from ketones and esters derived from higher homologues of

$$\underset{\text{Aldehyde}}{\begin{matrix}R\\H\end{matrix}\!\!>\!CO} + R'.MgX \longrightarrow \begin{matrix}R\\H\end{matrix}\!\!>\!C\!<\!\begin{matrix}R'\\OMgX\end{matrix} \xrightarrow{H_2O} \underset{\text{Secondary alcohol.}}{\begin{matrix}R\\H\end{matrix}\!\!>\!C\!<\!\begin{matrix}R'\\OH\end{matrix}} + Mg\!<\!\begin{matrix}OH\\X\end{matrix},$$

$$\underset{\text{Ketone}}{\begin{matrix}R\\R\end{matrix}\!\!>\!CO} + R'.MgX \longrightarrow \begin{matrix}R\\R\end{matrix}\!\!>\!C\!<\!\begin{matrix}R'\\OMgX\end{matrix} \xrightarrow{H_2O} \underset{\text{Tertiary alcohol.}}{\begin{matrix}R\\R\end{matrix}\!\!>\!C\!<\!\begin{matrix}R'\\OH\end{matrix}} + Mg\!<\!\begin{matrix}OH\\X\end{matrix}$$

formic acid. In the last case addition of the reagent is followed by double decomposition in which the alkoxy group is exchanged for an alkyl radical.

$$\begin{matrix}R\\EtO\end{matrix}\!\!>\!C:O \xrightarrow{R_1MgX} R.C\!<\!\begin{matrix}OMgX\\R_1\\OEt\end{matrix} \xrightarrow{R_1MgX} R.C\!<\!\begin{matrix}OMgX\\R_1\\R_1\end{matrix} + Mg\!<\!\begin{matrix}X\\OEt\end{matrix} \longrightarrow R.C\!<\!\begin{matrix}OH\\R_1\\R_1\end{matrix}$$

Tertiary alcohols are also formed together with ketones when carbon monoxide reacts with sodium alkyls.[3]

[1] Neuberg and Nord, *Ber.*, 1919, **52**, 2237. [2] The low yields often recorded for this reaction are said to be due to the production of formals, which can be readily decomposed by use of alcoholic hydrochloric acid to give 90 per cent. yields of the carbinols. N. Turkiewicz, *Ber.*, 1939, **72 B**, 1060. [3] Schlubach, *Ber.*, 1919, **52**, 1910.

Methyl alcohol, *methanol, carbinol* or *wood spirit*, CH_3OH, is found in the combined state in nature, *e.g.* in the form of methyl salicylate in oil of wintergreen, and as the methyl ester of anthranilic acid in oil of orange flowers.

It has long been prepared technically by the dry distillation of wood in iron retorts at the lowest practicable temperature. Under these conditions a certain amount of gas is produced, together with a fluid distillate consisting of an aqueous liquid (*pyroligneous acid*) and wood tar. Wood charcoal remains behind in the retort. The aqueous layer separating from the tar contains much water in addition to a number of other substances, chief among which are acetic acid, acetone and methyl alcohol. One hundred parts of wood yield a little more than one part of methyl alcohol. The acetic acid in the pyroligneous liquor is neutralised by the addition of lime, after which the methyl alcohol, acetone and a number of other substances of less importance are isolated by fractional distillation. The methyl alcohol may be rendered anhydrous by boiling it for some time with freshly prepared lime and then distilling several times over metallic calcium.[1]

Since 1923 methyl alcohol has been synthesised industrially from the carbon monoxide of water gas (*Patart* Process, Badische Anilin und Soda Fabrik).

$$CO+2H_2 = CH_3OH$$

The reduction is effected by means of hydrogen at high temperatures (450°) and pressures (200 atmos.) in the presence of catalysts (zinc oxide and chromium oxide). By varying the catalyst, *synthol*, a mixture of homologues of methanol, is produced.

Pure methyl alcohol is an inflammable liquid of boiling-point 64·6°, which is miscible in all proportions with water. In chemical behaviour it strongly resembles ethyl alcohol. On oxidation it is converted into formaldehyde, formic acid and finally carbon dioxide.

$$CH_3.OH \longrightarrow H.C\begin{matrix}=O\\ -H\end{matrix} \longrightarrow H.C\begin{matrix}=O\\ -OH\end{matrix} \longrightarrow CO_2+H_2O$$

Formaldehyde Formic acid.

Crude wood spirit is used technically for the denaturisation of alcohol (preparation of methylated spirits) and in the manufacture of aniline dye-stuffs and varnishes.

Ethyl alcohol, *ethanol, spirits of wine*, $CH_3.CH_2.OH$, is found occasionally in nature, *e.g.* as the butyric ester in unripe fruit of *heracleum giganteum* and in diabetic urine.

Formation and Preparation.—It may be obtained synthetically by the general methods of formation given above for primary alcohols. For example, ethylene unites with sulphuric acid to give ethyl hydrogen sulphate, which on hydrolysis with water yields ethyl alcohol.

$$C_2H_5.SO_4H+H_2O = C_2H_5.OH+H_2SO_4$$

As ethylene may be prepared from acetylene, and the latter from carbon and hydrogen, this reaction provides a complete synthesis of alcohol.[2]

[1] Metallic magnesium is also recommended for this purpose, N. Bjerrum and L. Zechmeister, *Ber.*, 1923, **56**, 894. [2] Berthelot, *C.*, 1899, **I**, 1018.

Alcohol is obtained industrially by fermentation processes based on the decomposition of various sugars, particularly grape sugar or glucose, $C_6H_{12}O_6$, in the presence of living yeast cells.

$$\underset{\text{Glucose}}{C_6H_{12}O_6} = 2\underset{\text{Ethyl alcohol.}}{C_2H_5.OH} + 2CO_2$$

In addition to ethyl alcohol a number of by-products are formed [1] which vary with the nature of the sugar employed and the conditions of fermentation. Prominent among these are the higher alcohols, especially amyl alcohol $C_5H_{11}.OH$, succinic acid, acetaldehyde and glycerol. Alcohol is obtained from the fermented liquid by distillation, and is brought on to the market under different names, according to the proportion of alcohol and the nature of the by-products present. Whisky or brandy contains 30 to 60 per cent. alcohol, and spirits and methylated spirits for domestic and industrial use 70 to 90 per cent. Higher concentrations are generally known briefly as alcohol.

The starting material for the manufacture of any one of these products is not glucose, but a less expensive substance from which glucose may be generated and subsequently fermented.

In all there are three sources of raw material available for the manufacture of alcohol or alcoholic beverages :

1. Starchy substances such as potatoes, corn, barley, rice.

2. Materials containing sugar, such as (*a*) fruit in which glucose is found (*e.g.* grapes, plums), (*b*) cane and beet sugar, or the molasses from their manufacture (p. 310), and (*c*) substances containing lactose.

3. Already fermented liquids, such as wine which is not otherwise saleable.

The most representative case is that in which starchy material forms the starting-point, when the following separate processes are to be distinguished in the production of alcohol. I. Formation of a solution containing sugars from the starchy raw material. II. Decomposition of the sugars in this liquid by fermentation. III. Distillation of alcoholic liquid from the fermented mash. IV. Final rectification of the distillate.

When the manufacture is based on one of the above raw products other than starch, the procedure is modified. In the fermentation of material containing sugar, process I is dropped out and process II becomes the starting-point. If we are concerned with the treatment of already fermented liquids, a beginning is made with process III.

In *Stage I* starch is converted by means of certain so-called *enzymes*

[1] Buchner and Meisenheimer, *Ber.*, 1904, **37**, 417 ; 1905, **38**, 620 ; 1906, **39**, 3201 ; 1910, **43**, 1773 ; 1912, **45**, 1633. Connstein and Lüdecke, *Ber.*, 1919, **52**, 1385. It is of the greatest practical and theoretical value to trace the intermediate products formed in the conversion of a carbohydrate into ethyl alcohol. The practical importance lies in the possibility of isolating the intermediate compounds or of diverting the course of the degradation process. The discovery described later, that glycerol may be prepared technically by carrying out the fermentation in the presence of sulphites, affords a good illustration of the manner in which the action of ferments may be controlled.

(see p. 148) into a sugar maltose, which, under the influence of other enzymes present in yeast, interacts with water to give glucose.[1]

$$\underset{\text{Maltose}}{C_{12}H_{22}O_{11}} + H_2O = 2\underset{\text{Glucose}}{C_6H_{12}O_6}$$

The former change is usually brought about on the industrial scale by means of *diastase*,[2] a white odourless and tasteless powder, the composition of which has not yet been accurately determined. It is produced during the germination of corn, and is found also in saliva and the juices of the pancreas, where it plays an important part in the digestive processes.

In the production of sugar from starch, diastase is not employed in the pure state but is used together with the whole corn in the form of *malt*, which is preferably obtained by the germination of barley. The simplest method of preparation is to allow the moist barley to germinate in the dark at 15°, in layers about 12 cm. high.

The malt is next mixed with water and unmalted corn, when the latter is transformed into sugar and the liquid or mash so obtained is then ready for fermentation. In another process, potatoes are converted into a thin homogeneous paste by treatment with superheated steam, and malt subsequently added. At a temperature of 60° to 62° the formation of maltose is complete in twenty minutes.

Stage II.—The sugar in the *mash* obtained in this manner is then fermented by the addition of yeast, and the fermentation allowed to proceed at a temperature not higher than 33°.[3] Fermentation of the mash occupies three to four days, and is accompanied by the evolution of carbon dioxide and consequent frothing of the liquid.

Very different views have been expressed as to the significance of the processes underlying alcoholic fermentation. Pasteur believed fermentation to be a purely physiological action, inseparably bound up with the life of the yeast cells and actuated by cellular metabolism.

Liebig, on the other hand, considered it to be a purely chemical change. The point was settled later by E. Buchner, who submitted a mixture of yeast and fine sand to strong pressure, disrupting the cell walls and obtaining an " expressed yeast juice " which no longer contained living cells, but nevertheless possessed strong fermentative power. This ability to induce fermentation was retained even after the liquid had been evaporated *in vacuo* and the dry mass again brought into solution.

The chemical changes taking place during fermentation are therefore due to the activity of this substance, named *zymase*, which belongs to the enzyme group, and has been shown by later investigations to be composed

[1] Since maltose is also a fermentable sugar, we may consider the two sugars maltose and glucose to be the immediate source of ethyl alcohol in the above process. [2] Starch may also be converted into sugar by heating with dilute sulphuric acid. [3] In addition to the alcoholic fermentation of saccharine liquids various other reactions are classed as fermentation processes. Milk sugar fermented with *bacterium lacticum* yields lactic acid, a reaction known as lactic fermentation and which causes the souring of milk in air (Buchner and Meisenheimer, *Ann.*, 1906, **349**, 125). Under the influence of *Bacillus butyricus* this lactic acid may be transformed into butyric acid (Buchner and Meisenheimer, *Ber.*, 1908, **41**, 1410). Succinic, citric, and other acids occurring in plants may also be obtained by fermentation.

of a number of individual enzymes. The yeast cells only participate in the process of fermentation in so far as they generate zymase. Alcoholic fermentation may therefore be defined as the change brought about by the action of zymase on certain sugars.

Buchner has also shown that other fermentation processes, such as lactic acid fermentation, are not produced by the fungi themselves but are due to the action of enzymes contained in them.[1]

Enzymes or unorganised ferments occur widely in plant and animal life and play an important part in metabolism, but little is known as to their chemical composition as few have been obtained in the pure state. Similarly, little can be said with certainty as to the mechanism of the reaction. In all probability they do not undergo decomposition themselves but develop their fermentative activity solely by catalytic action. It appears to be a characteristic property of the enzymes that each shows its activity towards one definite chemical compound alone. Emil Fischer, to whose work we owe much of our knowledge of these substances, has compared the relationship between enzyme and compound attacked to that between a key and its lock. This metaphor applies so completely that the enzyme does not even attack the stereoisomeride of the compound towards which it shows its activity. The selectivity is probably connected with the asymmetry of the enzyme molecule.

In the fermentation of saccharine fluids by living yeast certain other chemical changes take place, which may be ascribed to the life processes of the yeast itself. For this reason the simple chemical equation, according to which 100 parts of a sugar, $C_6H_{12}O_6$, should yield 51·11 parts of alcohol and 49·33 parts of carbon dioxide, is not strictly in accordance with the actual facts. Yeast uses up sugar in maintaining its life, and even with fermentation experiments on the small scale, in which all precautions are taken, there are obtained from 100 gms. pure sugar, $C_6H_{12}O_6$, no more than 48·49 gms. alcohol.

Later researches on the alcoholic fermentation of glucose[2] have shown it to be a process of extreme complexity, the mechanism of which is still under discussion. The following outline of the probable course of the reactions may therefore have to be modified in the light of further discoveries. Fermentation proceeds under the influence of a number of enzymes and through various intermediate phosphoric esters, whose importance has only recently been recognised. The key position among the latter is held by **glucose-1-phosphate** which appears to react in two main directions. On the one hand, in the presence of enzymes known as *phosphorylases* it is reversibly transformed into a polysaccharide, probably either glycogen or starch (see p. 318).

Glucose-1-phosphate $\rightleftarrows$ *Polysaccharide* + *free phosphate*

On the other hand, under the influence of various other enzyme systems glucose-1-phosphate is converted through a hexose-6-phosphate into **fructose-1:6-diphosphate** The latter then breaks down in the presence of the enzyme *aldolase*, yielding **phosphoglyceraldehyde** or phosphodihydroxyacetone.

$C_6H_{10}O_6(PO_3H_2)_2 \longrightarrow 2OHC.CHOH.CH_2OPO_3H_2$ or $2HOCH_2.CHOH.CH_2OPO_3H_2$

Fructose diphosphate — Phosphoglyceraldehyde — Phosphodihydroxyacetone.

In the next stage a dehydrogenating enzyme, *cozymase*, oxidises the phospho-

[1] See Note 3 on previous page. [2] C. Neuberg, *Biochem. Z.*, 1918, **92**, 234; *Ber.*, 1919, **52**, 1677. R. Willstätter, *Z. physiol. Chem.*, 1937, **247**, 269. G. Embden, *Klin. Wochschr.*, 1933, **12**, 213. O. Meyerhof, *Helv. chim. Acta*, 1935, **18**, 1030; *Bull. soc. chim. biol.*, 1938, **20**, 1335, 1345. R. Nilsson, *Biochem. Z.*, 1933, **258**, 198. For a recent survey see F. F. Nord, *Chem. Rev.*, 1940, **26**, 423.

glyceraldehyde to 3-phosphoglyceric acid and 2-phosphoglyceric acid, becoming itself changed into *dihydro-cozymase*.

$$\underset{\text{Phosphoglyceraldehyde}}{OHC.CHOH.CH_2OPO_3H_2} \longrightarrow \underset{\text{3-Phosphoglyceric acid}}{HOOC.CHOH.CH_2OPO_3H_2} \rightleftharpoons \underset{\text{2-Phosphoglyceric acid.}}{HOOC.CH(OPO_3H_2).CH_2OH}$$

By loss of water 2-phosphoglyceric acid yields **phosphopyruvic acid,**[1] which is then hydrolysed to **pyruvic acid.**

$$HOOC.CH(OPO_3H_2).CH_2OH \rightleftharpoons HOOC.C(OPO_3H_2):CH_2 \longrightarrow \underset{CH_3.CO.COOH}{HOOC.C(OH):CH_2}$$

Pyruvic acid and phosphoglyceric acid may readily be isolated from the fermenting liquid, the former by means of calcium carbonate and the latter by inhibiting further reaction by addition of sodium fluoride. Both compounds occupy important positions in recent theories of alcoholic fermentation.

In the last stage pyruvic acid breaks down in the presence of *carboxylase* to give carbon dioxide and acetaldehyde, and the aldehyde is finally stabilised by reduction to alcohol. The latter change is effected by the dihydro-cozymase previously formed, which gives up hydrogen and is thereby converted into cozymase again. Acetaldehyde may be detected in the fermenting liquor by addition of sodium bisulphite which serves to " fix " the aldehyde as it is produced.

Stage III.—From the fermented mash, in which the concentration of alcohol does not exceed 18 per cent., alcohol is removed by distillation. For this purpose stills are employed which permit the direct distillation of approximately 90 per cent. alcohol. The aqueous mass which remains behind in the distillation vessel is termed " spent wash," and is utilised as cattle food ; in it are to be found nearly all the proteins contained in the starting material.

Stage IV.—The raw spirit is next refined by rectification, at least four separate fractions being collected as follows :—

1. First runnings, *i.e.*, low-boiling by-products consisting mainly of acetaldehyde, boiling-point 20·8°.
2. Spirit of 93 per cent. ethyl alcohol.
3. Spirit of 90 per cent. ethyl alcohol.
4. Final runnings, *i.e.*, higher boiling products, containing amongst other compounds fermentation amyl alcohol (*fusel oil*), which consists of a mixture of isomeric alcohols of the formula $C_5H_{11}OH$.

For the preparation of alcohol of higher purity than 93 per cent. fractions 2 and 3 are again submitted to fractional distillation in special apparatus, whereby alcohol containing 99·9 per cent. is obtained.

Between operations III and IV, that is after the preparation of raw spirit and before refining, the liquid is sometimes filtered through charcoal to remove fusel oil.

Alcohol containing a small percentage (4 to 5) of water may also be rendered anhydrous by distillation over quicklime or barium oxide.

Attention has recently been drawn to the use of other raw material for the production of alcohol, such as wood, wood shavings and the sulphite liquor from the manufacture of cellulose. The latter is rich

[1] The pyruvic acid has been shown to be present *in vivo* only in the easily fermentable enolic form.

in the carbohydrate constituents of plant cells, particularly sugar, and after neutralisation may be fermented by a special kind of yeast to yield alcohol. Wood and wood shavings,[1] after hydrolysis by heating under pressure with dilute acids, yield 25 to 80 per cent. of soluble carbohydrate, of which 80 per cent. may be obtained as fermentable sugar. Another possible source of alcohol is in calcium carbide or acetylene. Under the catalytic influence of mercury salts, acetylene in warm acid solution combines with the elements of water to give acetaldehyde, which may then either be reduced to alcohol by use of nickel and hydrogen or oxidised to acetic acid (p. 196).

Properties.—Ethyl alcohol is a colourless mobile liquid with a pleasant, pungent smell. It boils at 78·3° and melts at −111·8°; sp. gr. 0·789 at 20°. Alcohol burns with a pale blue non-luminous flame. It is extremely hygroscopic and mixes in all proportions with water, when a contraction in volume takes place. The greatest diminution occurs when 53·9 vols. alcohol are added to 49·8 vols. water, the mixture occupying 100 vols. instead of 103·7. The concentration of aqueous solutions of alcohol may be ascertained by determining the specific gravity by the use of suitable hydrometers. In technical work the concentration is usually quoted in percentage by volume, and in scientific work in percentage by weight. Alcohol is an excellent solvent for many organic compounds such as resins and oils. It is readily oxidised, being converted first into aldehyde and then into acetic acid.

Uses.—In addition to extensive use as a beverage, alcohol is employed for a variety of industrial and scientific purposes. Owing to its value as a solvent for resins and dye-stuffs it is required in quantity for the preparation of colourless and coloured varnishes. It enters into the production of a number of coal-tar dyes, alkaloids and other preparations such as perfumes and collodion. As the starting material it functions in the preparation of numerous organic compounds such as ether, chloroform, chloral and fulminates of mercury and silver. In scientific laboratories it is one of the commonest solvents and is also used as a source of heat.

Alcohol intended for use as a beverage is usually heavily taxed and therefore expensive. On the other hand, alcohol for industrial purposes is now duty free in most countries, including Great Britain, where for many years the tax very seriously affected the industry in fine chemicals. Industrial alcohol, however, must first be denatured or rendered unfit for human consumption by the addition of certain substances. The denaturants may be crude wood spirit and pyridine bases, as in Germany; a mixture of wood naphtha, mineral naphtha and pyridine as in Great Britain; or benzene and wood spirit as in America. In addition, incompletely denatured alcohol (industrial methylated spirits), or alcohol containing special denaturants, is allowed for use in those industries where ordinary methylated spirits would be unsuitable.

[1] Tomlinson, *Chem. Trade Journ.*, 1918, **63**, 103; *C.*, 1919, **IV.**, 543.

Detection of Ethyl Alcohol.—On warming alcohol with iodine and potassium hydroxide, iodoform is produced (p. 133). This reaction is very sensitive, and by its use the presence of 1 part of alcohol in 2000 parts of water may be detected. Various other compounds, however, including acetone, also give this test.

Sodium ethoxide, *sodium ethylate*, C_2H_5ONa, is obtained by dissolving sodium in excess of absolute alcohol:

$$2C_2H_5.OH + 2Na = 2C_2H_5.ONa + H_2$$

It is readily soluble in alcohol, giving a solution which turns brown in air owing to oxidation. The pure compound forms a white powder and is frequently employed alone or in alcoholic solution as a condensing agent in organic synthesis.

Tribromoethyl alcohol, *Avertin*, $CBr_3.CH_2.OH$, is a white crystalline substance, m.p. 79 to 80°, which is used medicinally for inducing rectal narcosis.

Propyl alcohols, *propanols*, $C_3H_7.OH$. Both of the theoretically possible structural isomerides of this formula are known, viz.:—

$H_3C.CH_2.CH_2.OH$	and	$H_3C.CH(OH).CH_3$
Normal propyl alcohol,		*sec*-Propyl alcohol,
1-Propanol,		2-Propanol,
Ethyl carbinol		Dimethyl carbinol.

The constitution of both compounds follows from their behaviour on oxidation (see p. 140). Normal propyl alcohol on treatment with chromic acid is converted successively into propionaldehyde and propionic acid, showing it to be a primary alcohol; *sec*-propyl alcohol, on the other hand, yields acetone and is therefore a secondary alcohol.

Normal propyl alcohol, boiling-point 97°, sp. gr. 0·8044 at 20°, occurs in fusel oil, from which it is obtained by fractional distillation. In taste and smell it resembles ethyl alcohol.

***sec*-Propyl alcohol,** boiling-point 83°, sp. gr. 0·7887 at 20°, is best prepared from glycerol through the intermediate formation of *sec*-propyl iodide, $CH_3.CHI.CH_3$. It is also formed by the reduction of acetone with sodium amalgam, a further proof of the constitution given above.

Butyl alcohols, $C_4H_9.OH$. Four structural isomerides are theoretically possible, all of which are known.

1. **Normal butyl alcohol,** *propyl carbinol*, 1-*butanol*, $CH_3.CH_2.CH_2.CH_2OH$, is prepared by reducing butyric aldehyde, or by the fermentation of glycerol. On the large scale it is obtained, together with acetone, from inferior grades of maize by fermentation with *B. Clostridium acetobutylicum*. It is a colourless liquid, b.p. 116·8°, with a smell of both alcohol and fusel oil. On oxidation it yields butyric aldehyde and normal butyric acid, thus confirming the above formula, which may also be deduced from its method of synthesis.

2. **Secondary butyl alcohol,** *methyl ethyl carbinol*, 2-*butanol*, $CH_3.CH_2.CH(OH).CH_3$, may be obtained from methyl ethyl ketone by reducing it in moist ethereal solution with metallic sodium, or from the iodide $CH_3.CH_2.CHI.CH_3$ by the method indicated on p. 143. This iodide can be prepared from the alcohol erythritol, $C_4H_{10}O_4$, by the action of hydriodic acid. Secondary butyl alcohol is a colourless pleasant-smelling liquid, b.p. 98°. It is known in the *d*-, *l*- and *dl*-forms. On oxidation it yields methyl ethyl ketone, which on further oxidation yields acetic acid.

Optically active *sec*-butyl alcohols may be prepared by the method of Pickard and

Kenyon. The racemic alcohol is combined with phthalic anhydride to give butyl hydrogen phthalate, and this is then resolved by recrystallising the brucine salt. The active acid esters so obtained yield the active alcohols [1] on hydrolysis.

3. **Isobutyl alcohol,** *fermentation butyl alcohol, isopropylcarbinol, 2-methyl-3-propanol,* $(CH_3)_2CH.CH_2OH$, is formed in small amount during the alcoholic fermentation of sugar. It boils at 107° and is therefore found in fusel oil, particularly in that obtained from potato spirit. From this source it may be isolated by rectification in suitably designed columns. It is soluble to some extent in water, and in smell resembles both alcohol and fusel oil. On oxidation it first yields isobutyric aldehyde and then isobutyric acid.

4. **Tertiary butyl alcohol,** trimethyl carbinol, melts at 25°. It may be prepared by interaction of acetone with methyl magnesium halides :

$$(CH_3)_2CO + CH_3MgI \longrightarrow (CH_3)_3C.OMgI \xrightarrow{H_2O} (CH_3)_3C.OH$$

Amyl alcohols, $C_5H_{11}OH$, should exist according to theory in eight isomers, four of which are primary, three secondary, and one tertiary in structure. All of these are known.

1. $CH_3.CH_2.CH_2.CH_2.CH_2(OH)$, normal amyl alcohol, b.p. 137°.
2. $(CH_3)_2CH.CH_2.CH_2(OH)$, fermentation amyl alcohol, b.p. 131°.
3. $CH_3.CH(CH_2.CH_3).CH_2(OH)$, usually known as active amyl alcohol, b.p. 125°.
4. $(CH_3)_3C.CH_2(OH)$, tertiary butyl-carbinol, b.p. 112°.
5. $(C_2H_5)_2CH(OH)$, diethyl-carbinol, b.p. 117°.
6. $CH_3.CH_2.CH_2.CH(CH_3)(OH)$, methyl-*n*-propyl-carbinol, b.p. 119°.
7. $(CH_3)_2CH.CH(CH_3)(OH)$, methyl-isopropyl-carbinol, b.p. 112°.
8. $CH_3CH_2.C(CH_3)_2(OH)$, dimethyl-ethyl-carbinol, b.p. 102·5°.

Only those alcohols which possess special interest will be discussed here.

Fermentation amyl alcohol, isoamyl alcohol, $(CH_3)_2CH.CH_2.CH_2OH$, b.p. 131°, is the chief constituent of fusel oil. The name is derived from starch (*amylum*), these alcohols having been first isolated as by-products in the fermentation of starch to ethyl alcohol. Ehrlich [2] has shown that the production of fusel oil during fermentation is a result of the protein-forming activity of the living yeast cells and is due to the disruption of certain amino-acids, particularly leucine, isoleucine and valine, by the yeast to satisfy its need for nitrogen and for the production of zymase. The corresponding higher alcohols are left behind as non-assimilable products of metabolism. In this way *l*-leucine gives rise to inactive isoamyl alcohol, *l*-isoleucine to laevorotatory amyl alcohol, and valine to isobutyl alcohol. It is probable that the other alcohols which occur to a smaller extent in fusel oil are also derived from amino-acids.

$$\underset{\text{}}{(CH_3)_2CH.CH_2.CH(NH_2).CO_2H} + H_2O = \underset{\text{Inactive isoamyl alcohol.}}{(CH_3)_2CH.CH_2.CH_2OH} + CO_2 + NH_3$$

l-Leucine.

[1] Pickard and Kenyon, *J. C. S.*, 1913, **103**, 1938. [2] F. Ehrlich, *Ber.*, 1907, **40**, 1027.

The earlier view that amyl alcohol was produced during fermentation by the action of bacteria on sugar has therefore proved incorrect. The chief sources of fusel oil are the amino-acids already present as such in the natural mash and those produced from proteins of the raw material during the conversion of the malt into sugar. The proteins contained in the yeast play very little part in the formation of fusel oil.

A practical outcome of the above is that the content of fusel oil in raw spirit may be increased by the addition of leucines and their homologues to the fermenting mash. On the other hand, by the addition of sufficient amounts of other nitrogenous compounds which are easily assimilable by the yeast, the formation of higher alcohols during fermentation may be almost completely avoided. Amyl alcohol is a valuable article of commerce owing to its numerous technical applications, *e.g.*, as a solvent in the manufacture of varnish, and in the form of amyl acetate and other esters in the confectionery, mineral water and fruit essence industries.

Fermentation amyl alcohol is always accompanied by **laevorotatory amyl alcohol,** 2-methyl-1-butanol, $CH_3.CH_2.CH(CH_3).CH_2OH$, which is of interest as one of the simplest examples of an optically active compound. Pure *d*-amyl alcohol[1] (2-methyl-1-butanol) has $[\alpha]_D - 5{\cdot}83°$. The proportion of optically active alcohol in the commercial alcohol is very variable.

The problem of separating these two products, the output of which amounts to thousands of tons per annum, was solved by Marckwald.[2] An examination of the fusel oils isolated from the spirit prepared from potatoes, corn and beet sugar molasses respectively, with reference to the relative amounts of amyl alcohols present, showed that a productive source of active amyl alcohol was to be found in the fusel oil from molasses. The proportion of active alcohol in the latter varies between 48 and 58 per cent. One of the methods of separation worked out by Marckwald was based on earlier experiments of Pasteur, the two alcohols being converted first into the amyl sulphuric acids, the mixed barium salts of which may be separated by fractional crystallisation and the pure alcohols regenerated from the individual salts. Although the two salts form an unbroken series of mixed crystals, their separation may be effected completely and comparatively easily by careful fractional crystallisation.

The separation of the amyl alcohols of fusel oil may also be effected by conversion into the solid esters of 3-nitrophthalic acid and subsequent fractional crystallisation.

Dimethyl-ethyl-carbinol, *tertiary amyl alcohol, amylene hydrate,* $(CH_3)_2C(OH).C_2H_5$, is a liquid with a smell like camphor. It is used as a hypnotic and is prepared industrially from fermentation amyl alcohol. When the latter is distilled with zinc chloride, water is split off and a mixture of isomeric amylenes of the formula C_5H_{10} obtained. On being shaken with aqueous sulphuric acid at $-20°$ this is partly dissolved, giving a solution of the acid sulphate of *tert.* amyl alcohol, which on subsequent dilution and distillation yields the alcohol itself. *Trimethyl-ethylene* (b.p. 37°), an amylene of the formula $(CH_3)_2C:CH.CH_3$, is prepared by heating the alcohol to 200° and is used as a narcotic under the name of *pental.*

[1] Although laevorotatory, the alcohol is generally termed *d*-amyl alcohol as most of its derivatives have a dextro rotation. For derivatives of amyl alcohol compare O. Aschan, *C.* 1918, **II**, 939. [2] *Ber.*, 1901, **34**, 479, 485; 1902, **35**, 1595; 1904, **37**, 1038; 1909, **42**, 1583.

Among the higher alcohols only cetyl alcohol and myricyl alcohol need be mentioned.

Cetyl alcohol, *hexadecyl alcohol*, $C_{16}H_{33}OH$, occurs as the palmitic ester in spermaceti, from which it is obtained by hydrolysis with alcoholic potash. It is a white crystalline mass of melting-point 49·5°. *Sodium cetyl sulphate* (see p. 201) may be used as a synthetic detergent in place of soap.

Myricyl or **melissyl alcohol,** $C_{30}H_{61}OH$, is found as the palmitic ester in bees-wax and melts at 85°.

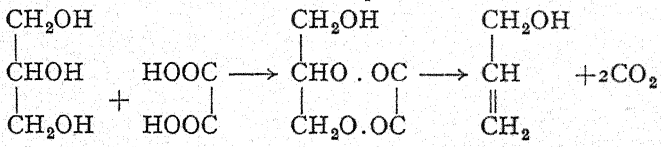
UNSATURATED MONOHYDRIC ALCOHOLS

These may be derived from the olefins or acetylenes, and consequently show on the one hand the behaviour typical of the saturated alcohols, and on the other the additive properties of the unsaturated hydrocarbons.

It should be remembered that the grouping : C : CH.OH is unstable and readily passes over into the group : CH.CH : O (see p. 62) ; *i.e.* the alcohols in which the hydroxyl group is attached to a doubly bound carbon atom are for the most part unstable and isomerise into the corresponding aldehydes. An example of this type is **vinyl alcohol,** ethenol, $CH_2 : CH.OH$, traces of which are supposed to be present in commercial ether.

This alcohol is not known in the pure state, but has been found to occur as an intermediate in the slow oxidation of ethylene, under which conditions it exists in equilibrium with its two isomerides ethylene oxide and acetaldehyde.[1] Vinyl alcohol may be isolated from this mixture in the form of its double compound with mercury oxychloride.

On the other hand, unsaturated alcohols in which the hydroxyl group is united to a singly bound carbon atom are stable and are known in large number. One of the most important of these is **allyl alcohol,**



3-propenol, $CH_2 : CH.CH_2OH$, which occurs in raw wood spirit (0·1 to 0·2 per cent.). It may be prepared from allyl iodide by heating with water to 100°, or more conveniently from glycerol by heating to 260° with oxalic acid. As has been shown by Chattaway, this reaction involves the formation of a neutral glyceryl oxalate and its decomposition by heat into CO_2 and allyl alcohol. When oxidised under certain conditions it yields first acrylic aldehyde or acroleïn and then acrylic acid, showing it to be a primary alcohol.

$$\underset{\text{Allyl alcohol}}{H_2C : CH.CH_2OH} \longrightarrow \underset{\text{Acroleïn}}{H_2C : CH.CH : O} \longrightarrow \underset{\text{Acrylic acid.}}{H_2C : CH.COOH}$$

On oxidation with dilute aqueous potassium permanganate, two hydroxyl groups are added to the allyl alcohol molecule, transforming it into glycerol :

$$\underset{\text{Allyl alcohol}}{H_2C : CH.CH_2OH} \xrightarrow{H_2O+O} \underset{\text{Glycerol.}}{CH_2OH.CHOH.CH_2OH}$$

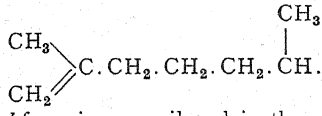
[1] D. M. Newitt, see W. A. Bone, *J. C. S.*, 1933, 1604.

Allyl alcohol is a pungent-smelling liquid, b.p. 96°; at −50° it solidifies to a mass of crystals. It unites with hydrogen and halogens, and forms an ozonide with ozone. The latter is an unstable syrup which decomposes at room temperature and on boiling with water is hydrolysed to yield an aldehyde (see p. 121).

A number of unsaturated alcohols and their corresponding aldehydes are found in the essential oils of plants associated with cyelic terpenes (p. 472), to which they are closely related in structure. Hence they are known as *olefinic* or *open-chain terpene alcohols*. Well-known examples of this class are *geraniol*, *nerol* and *citronellol*.

Geraniol, $(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.CH_2OH$, is a pleasant-smelling liquid, b.p. 121°/17 mm. It may be isolated from geranium oil or prepared by the reduction of the aldehyde citral, into which it is again transformed on oxidation. As will be seen later, it yields the cyclic terpene derivative *terpin*, p. 476, on treatment with dilute sulphuric acid.

Geraniol is the chief constituent of geranium oil, rose oil and lemon-grass oil. **Nerol** appears to be a geometrical isomeride of geraniol. It has an odour of roses and is a valuable constituent of perfumes. **Citronellol,**

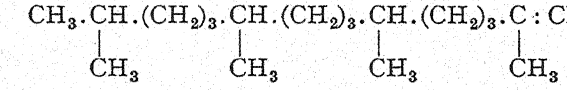


$CH_3.C(=CH_2).CH_2.CH_2.CH(CH_3).CH_2.CH_2OH$, b.p. 117 to 118°/17 mm., occurs in the *l*-form in rose oil and in the *d*-form in citronella oil. As in many other compounds of this type, the terminal group

$CH_3.C(=CH_2)$ readily isomerises into

$(CH_3)_2C:$ under the influence of reagents.

Phytol, $C_{20}H_{39}OH$, is one of the higher unsaturated alcohols. It possesses special interest as standing in close relationship to chlorophyll (the green colouring matter of leaves), from which it has been isolated by Willstätter.[1] When chlorophyll is treated in cold alcoholic solution with oxalic acid the atom of magnesium which is an integral part of the complex molecule is replaced by two atoms of hydrogen, and a wax-like substance called *phaeophytin* produced. The latter is an ester, and on hydrolysis with cold alcoholic potash gives the alcohol phytol, $C_{20}H_{39}OH$. Phytol is a colourless oil, which cannot be distilled without decomposition except at extremely low pressures. It boils at 145° under 0·03 mm. pressure, and has the following structure[2]:



$CH_3.CH(CH_3).(CH_2)_3.CH(CH_3).(CH_2)_3.CH(CH_3).(CH_2)_3.C(CH_3):CH.CH_2OH$

Propargyl alcohol, 3-propinol, $CH:C.CH_2OH$, is an example of an alcohol derived from a hydrocarbon of the acetylene series. It is obtained from monobromoallyl alcohol by removing hydrogen bromide with potash. It is a pleasant-smelling liquid of boiling-point 114°, which directly adds on four atoms of bromine, and like the acetylene hydrocarbons yields explosive metallic compounds with ammoniacal solutions of cuprous chloride or silver nitrate.

[1] Willstätter and Hocheder, *Ann.*, 1907, **354**, 205. [2] F. G. Fischer and K. Löwenberg, *Ann.*, 1928, **464**, 69; 1929, **475**, 183.

V

Esters of Monohydric Alcohols with Inorganic Acids

As already mentioned on p. 139, *esters* may be compared to metallic salts and are produced by the union of acids and alcohols with simultaneous liberation of water. Corresponding to halide salts are the esters of halogen acids, already treated on p. 129 under the heading of monohalogen substitution products of the hydrocarbons. Esters are also known of other mineral acids. Polybasic acids give rise to several series of esters in the same manner as they form several series of salts.

When the total replaceable hydrogen of an acid is displaced by alkyl groups, neutral esters are formed, corresponding to neutral salts. These esters are mostly liquids of neutral reaction, often of very pleasant odour and almost or completely insoluble in water.

If, on the other hand, the replaceable hydrogen of a polybasic acid is incompletely substituted by alkyl groups, an *acid ester* or ester-acid is produced. Acid esters are genuine acids and capable of exchanging the as yet unreplaced hydrogen for metals in the usual manner. They are considerably less stable than the normal esters, are odourless and generally dissolve readily in water.

$C_2H_5HSO_4$	$(C_2H_5)_2SO_4$
Ethyl hydrogen sulphate	Diethyl sulphate.

All esters are *hydrolysed* on heating with sodium or potassium hydroxide, or by treatment with superheated steam, when they break up into the alcohol and acid from which they are derived. The former process has long been employed in the manufacture of soaps from fats and is therefore known as **saponification.** Acid esters are often hydrolysed to the free acid and alcohol merely on being mixed with water at the ordinary temperature, but the action occurs more readily on boiling.

$$C_2H_5NO_3+KOH = C_2H_5.OH+KNO_3$$
$$C_2H_5HSO_4+H_2O = C_2H_5.OH+H_2SO_4$$

Methods of Formation.—1. Frequently by direct interaction of acid and alcohol.

$$CH_3.OH+HCl = CH_3Cl+H_2O$$

Under these conditions polybasic acids first give rise to the acid esters.

In this case there is no quantitative conversion of alcohol and acid into ester, but the formation of the latter ceases at a certain point. This state of affairs is brought about by the hydrolytic action of the water liberated, and leads eventually to a state of equilibrium. By employing an excess of acid or by removing the ester from the reaction mixture (*e.g.* by continuous distillation) a larger yield may be attained.

2. By the action of silver salts of the acids on alkyl halides.[1]

$$C_2H_5I+AgNO_3 = C_2H_5NO_3+AgI$$

[1] Sometimes an isomeride of the expected ester is obtained by this method.

3. By double decomposition between acid chlorides and alcohols or preferably sodium alcoholates.

$$SO_2Cl_2+2C_2H_5OH = SO_2(OC_2H_5)_2+2HCl$$

Among the numerous esters of mineral acids the most interesting are those of sulphuric acid.

Esters of Sulphuric Acid

Acid esters of sulphuric acid, $RHSO_4$, usually termed alkyl hydrogen sulphates, are produced on mixing alcohols with concentrated sulphuric acid or by the union of ethylene hydrocarbons with concentrated sulphuric acid (p. 120).

$$SO_2(OH)_2+C_2H_5.OH = SO_2\begin{matrix}OC_2H_5\\OH\end{matrix}+H_2O$$

They possess a strong acid reaction, and their salts are, for the most part, readily soluble in water. Among the latter the alkali salts crystallise well, and are used in a variety of reactions. For example, ethyl bromide is conveniently prepared by the dry distillation of a mixture of potassium ethyl sulphate and potassium bromide.

$$KO.SO_2.OC_2H_5+KBr = KO.SO_2.OK+C_2H_5Br$$

The alkali salts yield mercaptans when heated with potassium hydrosulphide, thio-ethers with potassium sulphide, and alkyl cyanides with potassium cyanide.

Neutral esters of sulphuric acid, R_2SO_4, are produced by the distillation of alkyl sulphuric acids, by heating alcohols with sulphuric acid, or alkyl iodides with silver sulphate. The most important neutral ester is **dimethyl sulphate,** which is used industrially and in the laboratory as a methylating agent.[1] It may be prepared by the decomposition of methyl hydrogen sulphate by distillation at a high temperature, or by

$$SO_2\begin{matrix}OCH_3\\OH\end{matrix}+SO_2\begin{matrix}OH\\OCH_3\end{matrix} = SO_2\begin{matrix}OCH_3\\OCH_3\end{matrix}+SO_2\begin{matrix}OH\\OH\end{matrix}$$

Methyl hydrogen sulphate — Dimethyl sulphate.

adding the required amount of sulphur trioxide to cooled methyl alcohol,

$$2CH_3OH+2SO_3 = (CH_3)_2SO_4+H_2SO_4.$$

Methyl hydrogen sulphate is obtained by treating methyl alcohol with chlorosulphonic acid or fuming sulphuric acid.

Dimethyl sulphate boils at 188°, strongly attacks the mucous membranes and is poisonous. It is a valuable methylating agent and may be substituted in all cases for methyl iodide, although under the usual experimental conditions only one of the two methyl groups is utilised. In general it reacts with much greater rapidity and gives better yields than methyl iodide. It is especially effective for the methylation of phenols.

[1] For the methylation of sugars see W. N. Haworth, *J. C. S.*, 1915, **107**, 8.

When an alkaline solution of phenol is shaken for a short time with a molecular proportion of dimethyl sulphate, the phenol is practically quantitatively methylated.

$$\underset{\text{Sodium phenate}}{C_6H_5ONa} + (CH_3)_2SO_4 = \underset{\text{Anisole.}}{C_6H_5OCH_3} + NaCH_3SO_4$$

Esters of nitric acid are produced by the action of alcohols on concentrated nitric acid, free from oxides of nitrogen. They are mobile liquids which are practically insoluble in water, and explode when rapidly heated.

The **esters of nitrous acid**, R.O.NO, are isomeric with the nitroparaffins, $R.NO_2$, and of these only the isoamyl ester, $C_5H_{11}.O.NO$, usually known as *amyl nitrite*, need be mentioned. It is prepared by leading nitrogen trioxide into hot amyl alcohol, and is a yellow liquid, b.p. 98°. It is employed in medicine (*amyl nitris*) on account of its property of expanding the blood vessels and relaxing the contractile muscles. It is also used for preparing nitroso- and diazo-compounds.

Among less common inorganic esters, those of phosphoric acid are of considerable value in the investigation of naturally occurring phosphorus compounds of physiological importance (see nucleic acids).

VI

Ethers

Ethers may be considered to be anhydrides of the alcohols in the same way as metallic oxides are anhydrides of the corresponding hydroxides. According to whether the alkyl radicals united to the oxygen atom are similar or dissimilar, the compounds are known as *simple* or *mixed ethers*.

$C_2H_5.O.C_2H_5$	$C_2H_5.O.CH_3$
Diethyl ether	Methyl ethyl ether
(Simple ether)	(Mixed ether).

They may be prepared :

1. By the interaction of sodium alcoholates with alkyl halides in alcoholic solution. By this synthesis the structure of the ethers was first

$$C_2H_5.O.Na + I.CH_3 = C_2H_5.O.CH_3 + NaI$$

established by Williamson.

2. By the action of sulphuric acid on alcohols. This method of formation, which is described in detail below, is of great practical importance, although it only gives satisfactory yields up to dipropyl ether. With higher alcohols water tends to split off to form unsaturated hydrocarbons of the ethylene series.

3. Sabatier and Mailhe[1] have developed a general method for preparing esters and ethers, depending on the catalytic action of certain metallic oxides. In this reaction an unstable alcoholate of the metal is produced as an intermediate product. If the vapour of ethyl alcohol is

[1] See also Mailhe and de Godon, *Bull. Soc.*, 1920 [iv.], **27**, 121.

led over precipitated alumina at temperatures between 240° and 260°, the dehydration of the alcohol does not result in the formation of ethylene, $C_2H_5OH=H_2O+C_2H_4$, but extends over two molecules of alcohol to give ether, $2C_2H_5OH=H_2O+(C_2H_5)_2O$. Methyl ether, $CH_3.O.CH_3$, is obtained even more readily under these conditions, since the formation of an ethylene hydrocarbon is not possible in this case. The unstable alcoholate $(CH_3O)_6Al_2$ is transformed immediately into $Al_2O_3+3(CH_3)_2O$. Titanium oxide, TiO_2, thorium oxide, ThO_2, and the blue oxide of tungsten, W_2O_5, may also be used as catalysts.

The above is an example of the simple and convenient syntheses which have recently been effected with the aid of metallic oxides as catalysts. In a similar manner it is possible to synthesise ethylene hydrocarbons, aldehydes, ketones, thio-alcohols and primary and secondary amines.

4. By double decomposition between alkyl halides and silver oxide.

$$2C_2H_5I+Ag_2O = (C_2H_5)_2O+2AgI$$

Ethers are very mobile liquids of neutral reaction and are only sparingly soluble in water. They are inactive in a chemical sense and are relatively stable towards acids and alkalis.

Ether, ethyl ether, $(C_2H_5)_2O$, is by far the best known and most important compound of this series. It is prepared technically and in the laboratory[1] by heating a mixture of nine parts of concentrated sulphuric acid and five parts of 90 per cent. alcohol to a temperature of 135° to 140°. Ether and water distil over, and a continuous supply

$$2C_2H_5OH \longrightarrow (C_2H_5)_2O+H_2O$$

of alcohol is allowed to flow into the distillation vessel, where it is immediately acted upon by the sulphuric acid. The course of the reaction was explained by Williamson by the following equations :

I. $C_2H_5.OH+H_2SO_4 = C_2H_5OSO_3H+H_2O$
Ethyl hydrogen sulphate.

II. $C_2H_5.OSO_3H+H.O.C_2H_5 = C_2H_5.O.C_2H_5+H_2SO_4$

Hence it would be expected that small amounts of sulphuric acid should be capable of converting unlimited quantities of alcohol into ether. In practice, however, this cannot be realised, owing to dilution of the acid by the liberated water and the incidence of by-reactions.

Van Alphen[2] has shown that Williamson's theory of ether formation in the presence of sulphuric acid must be modified in the light of further research. Ethyl alcohol may be converted into ether by heating it with any acid which is of sufficient strength, *e.g.* arsenic, phosphoric, sulphurous, picric and chloracetic acids, as well as benzene sulphonic acid, hydrochloric acid and hydriodic acid. Many salts of weak organic and inorganic bases with strong acids are also effective, such as morphine hydrochloride and ferric sulphate.

Two points are of special importance in this connection : (*a*) the use

[1] For the catalytic preparation of ether in the dry way see Mailhe and de Godon, *Bull. Soc.*, 1919 [iv.], **25**, 565. [2] J. van Alphen, *Rec. Trav. Chim.*, 1930, **49**, 756.

of ferric sulphate for 8 hours at 155° gives the same final equilibrium mixture, whether the starting-point is alcohol or an equimolecular mixture of ether and water, (*b*) hydrochloric acid is also a good catalyst at 155°, but the reaction cannot proceed according to Williamson's scheme,

$$C_2H_5OH+HCl \longrightarrow C_2H_5.Cl+H_2O$$
$$C_2H_5OH+C_2H_5Cl \longrightarrow (C_2H_5)_2O+HCl$$

because at this temperature ethyl chloride does not react with alcohol.

The conversion of alcohol into ether is thus an equilibrium reaction which is catalysed by $H^+(H_3O^+)$ ions, the reaction becoming appreciable at 100° and upwards. The change may be classed with other reactions

$$2C_2H_5OH \rightleftharpoons (C_2H_5)_2O+H_2O$$

of the type $\geqslant C-O-C\leqslant +H_2O \rightleftharpoons \geqslant C\cdot OH+HO\cdot C\leqslant$ which are catalysed by hydrogen ion, such as the esterification of acids, the hydrolysis of esters and the formation of acetals and lactones.[1]

Sulphuric acid is an excellent catalyst not only because it is relatively non-volatile and a strong acid, but because it yields an ester, ethyl hydrogen sulphate, which unlike ethyl chloride is also non-volatile and a strong acid. This ester therefore remains in the reaction mixture, where it functions as an additional catalyst.

The crude ether prepared in the above manner is allowed to stand for some time over quicklime to free it from water, alcohol and sulphur dioxide, after which the ether is distilled off on a water-bath at 50°. In order to remove the last traces of alcohol it may be repeatedly shaken with small quantities of water, dried over calcium chloride and finally distilled over sodium.

Properties and Uses.—Ethyl ether is a colourless, extremely mobile liquid, lighter than water and of characteristic smell. It boils at 35·6° and solidifies at −113°. It is miscible in all proportions with alcohol but is only sparingly soluble in water. One volume of ether dissolves in about eleven volumes of water at 25°, and at the same time the water dissolves to some extent in the ether. A large number of carbon compounds, such as hydrocarbons and fats, are insoluble in water but dissolve readily in ether, which is therefore employed extensively as a solvent in organic chemistry. Ether burns with a luminous flame. It is highly inflammable and its vapour forms an explosive mixture with air. When inhaled for some time it brings about loss of consciousness, and like chloroform it is used as an anæsthetic in surgical operations.

Ether combines with hydro-ferrocyanic, hydro-ferricyanic and cobalticyanic acids. According to Baeyer and Villiger,[2] this is due to the formation of a tetravalent oxygen compound.

Ether unites with bromine to give an unstable crystalline compound $C_4H_{10}OBr_8$, melting at 24°.

[1] For a more detailed explanation see L. Hammett, *Physical Organic Chemistry*, p. 299 (McGraw-Hill Book Co., 1940). [2] Baeyer and Villiger, *Ber.*, 1901, **34**, 2688. Compare also Cohen and Gatecliff, *Proc. Chem. Soc.*, 1904, **20**, 194. McIntosh, *J. Am. C. S.*, 1908, **30**, 1097.

VII

Thio-alcohols and Thio-ethers

If the oxygen in an alcohol is replaced by sulphur, the resulting compound is known as a **thio-alcohol, mercaptan** or **hydrosulphide.** An example of this type is CH_3SH, methyl mercaptan or methyl hydrosulphide. As may be seen from their properties, these compounds bear the same relation to hydrogen sulphide as the alcohols to water. While strongly resembling the alcohols they also exhibit weak acidic properties, as would be expected from their derivation from hydrogen sulphide. When they are treated with metallic oxides, such as mercuric oxide, the hydrogen of the —SH group is replaced by metal. Hence the name mercaptan (*mercurium captans*). With mineral acids the metallic derivatives or mercaptides regenerate the free mercaptan.

Mercaptans may be obtained by warming alkyl halides or salts of an alkylsulphuric acid with potassium hydrosulphide,

$$CH_3I+KSH = CH_3SH+KI$$
$$C_2H_5SO_4K+KSH = C_2H_5SH+K_2SO_4$$

by the action of phosphorus pentasulphide on alcohols,

$$5C_2H_5OH+P_2S_5 = 5C_2H_5SH+P_2O_5$$

or by the biochemical reduction of the corresponding thio-aldehydes with living yeast. Thio-aldehydes are not easily prepared in the pure state, but as they are readily formed from ordinary aldehydes it is sufficient for this purpose to bring the latter under suitable conditions into an alcoholic solution of hydrogen sulphide and ammonia (ammonium sulphide), and to submit this mixture to the action of fermenting yeast.[1]

Mercaptans have an extremely nauseous smell and boil at much lower temperatures than the corresponding alcohols. Like hydrogen sulphide they are readily attacked by oxidising agents. For example, under the influence of atmospheric oxygen they are converted into disulphides.

$$2C_2H_5SH+O = C_2H_5S.SC_2H_5+H_2O$$

Nitric acid transforms them into sulphonic acids

$$C_2H_5SH+3O = C_2H_5.SO_3H$$

Ethyl-sulphonic acid.

The presence of mercaptans may be detected by means of the intensely coloured *nitrosyl mercaptides* they form with nitrous acid.[2]

Mercaptans combine with aldehydes to form mercaptals of the type of $CH_3.CH(SC_2H_5)_2$ and with ketones to form mercaptols such as $(CH_3)_2C(SC_2H_5)_2$. They also form additive compounds with unsaturated hydrocarbons.[3]

Ethyl mercaptan, C_2H_5SH, commonly known as *mercaptan*, is the most important representative of this class.[4] It is obtained technically

[1] C. Neuberg and F. Nord, *Ber.*, 1914, **47**, 2264. F. Nord, *Ber.*, 1919, **52**, 1207. [2] H. Rheinboldt, *Ber.*, 1927, **60**, 184. [3] Posner, *Ber.*, 1905, **38**, 646. [4] Methyl mercaptan, CH_3SH, has been isolated as a cleavage product in the fermentation of proteins.

from ethyl chloride and potassium hydrosulphide, and is used in the preparation of sulphonal. Ethyl mercaptan is a particularly evil-smelling liquid of boiling-point 36°. It dissolves sparingly in water, and in air rapidly oxidises to ethyl disulphide, $(C_2H_5)_2S_2$.

Mercaptan condenses with acetone with elimination of water according to the equation,

$$\underset{\text{Acetone}}{(CH_3)_2CO} + 2\underset{\substack{\text{Ethyl}\\\text{mercaptan}}}{HSC_2H_5} = \underset{\substack{\text{Dimethyl-diethyl-}\\\text{mercaptol.}}}{(CH_3)_2C(SC_2H_5)_2} + H_2O$$

When the product of condensation is oxidised with potassium permanganate it yields diethylsulphone-dimethylmethane (acetone-diethylsulphone), $(CH_3)_2C(SO_2C_2H_5)_2$, which is employed as a hypnotic under the name of **sulphonal.** This crystallises in colourless prisms, is very sparingly soluble in water and melts at 126°.

Trional, $\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>\!C(SO_2C_2H_5)_2$, m.p. 75°;

and **tetronal,** $\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!\!>\!C(SO_2C_2H_5)_2$, m.p. 85°, are prepared in a corresponding manner to the above and possess similar properties.

Thio-ethers or *alkyl sulphides*, such as methyl sulphide, $(CH_3)_2S$, are formed by heating potassium sulphide, K_2S, with an alkyl iodide.

$$2CH_3I + K_2S = (CH_3)_2S + 2KI$$
$$2C_2H_5SO_4K + K_2S = (C_2H_5)_2S + 2K_2SO_4$$

ββ′-Dichloroethyl sulphide (*Mustard gas*), $(ClCH_2.CH_2)_2S$, has been used as a poison gas in warfare, and among other methods may be prepared by the following reaction [1]:

$$2CH_2{:}CH_2 + S_2Cl_2 = (CH_2Cl.CH_2)_2S + S$$

Thio-ethers are neutral volatile liquids of nauseous smell. With metallic salts they yield double compounds of the type $(C_2H_5)_2S,HgCl_2$.

With mild oxidising agents one atom of oxygen is taken up to form *sulphoxides*. Under more vigorous oxidation two atoms of oxygen enter the molecule with the formation of *sulphones*.

$$(CH_3)_2S \longrightarrow (CH_3)_2SO \longrightarrow (CH_3)_2SO_2$$

Alkyl Polysulphides. — If in the method given above for the preparation of thio-ethers from potassium sulphide and alkyl halides a polysulphide of potassium is exchanged for the sulphide, the reaction leads to the formation of the corresponding polysulphides, such as methyl disulphide, $(CH_3)_2S_2$, and methyl trisulphide, $(CH_3)_2S_3$. These are yellow liquids of unpleasant smell, which readily undergo oxidation.

Allyl disulphide, $(C_3H_5)_2S_2$, one of the best known polysulphides, occurs together with related polysulphides in garlic.

Compounds of selenium and tellurium are also known corresponding to the foregoing sulphur derivatives. They resemble the latter in their chemical properties but are of less theoretical and practical importance.

[1] W. J. Pope, *Chem. Trade Journal*, 1919, 64, 477. Smith, Clowes and Marshall, *C.*, 1919, III, 622. For other poison gases see *The War Gases* by M. Sartori (Churchill, 1939).

VIII

Alkyl Nitrogen Compounds

I.—NITROSO-DERIVATIVES

Nitroso-compounds are those in which the nitroso group —N : O is united to a hydrocarbon radical. They may be obtained by the following methods :—

1. By treating oximes with an oxidising agent such as bromine dissolved in pyridine, or chlorine in hydrochloric acid. The change occurs with greater ease when the carbon atom attached to the nitrogen simultaneously passes over into the tertiary condition. For instance, the reaction between acetoxime and bromine proceeds according to the equation,[1]

$$(CH_3)_2C:NOH + Br_2 \longrightarrow (CH_3)_2C\begin{matrix}NO\\Br\end{matrix} + HBr$$

Acetoxime — Bromo-nitroso-propane.

2. By oxidising an amine containing a tertiary carbon atom with Caro's acid (monopersulphuric acid). In this manner tertiary nitroso-butane is obtained from tertiary butylamine.

$$(CH_3)_3C.NH_2 \longrightarrow (CH_3)_3C.NHOH \longrightarrow (CH_3)_3C.NO$$

3. Nitroso-compounds containing other substituents in the molecule in addition to the nitroso group are formed by the action of nitrogen peroxide, nitrogen trioxide, nitrosyl chloride or nitrosyl bromide on ethylene hydrocarbons (see p. 120).

Properties.—True nitroso-compounds can exist in two modifications, one of which is dimolecular, colourless and solid, and the other monomolecular, blue and often liquid. The typical nitroso-derivatives are monomolecular liquids or crystalline solids of deep blue colour. They are highly volatile and have a characteristic and usually pungent smell. The colourless crystalline dimolecular forms give blue oils on fusion, and under suitable conditions dissolve with the production of a blue solution.[2]

Nitroso-butane, $(CH_3)_3C.NO$, for example, exists as a blue compound of the formula C_4H_9NO, and as a colourless modification of the formula $C_8H_{18}N_2O_2$. In solution, the latter undergoes partial dissociation, which increases with rise of temperature.

[1] Piloty, *Ber.*, 1898, **31**, 452 ; 1902, **35**, 3113. On treating ketoximes with bromine in the presence of pyridine a blue coloration is produced even at high dilutions, owing to the formation of bromo-nitroso-compounds. This reaction is an excellent test for the detection of aliphatic ketones, particularly acetone. [2] Piloty, *Ber.*, 1902, **35**, 3114. J. Schmidt, *Ber.*, 1902, **35**, 2323, 3727. Bamberger and Seligmann, *Ber.*, 1903, **36**, 685.

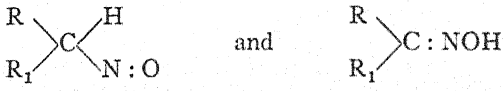
Nitroso-compounds may be oxidised to nitro-compounds and reduced to amines,

$$(CH_3)_3C.NH_2 \xleftarrow{\text{Reduction}} (CH_3)_3C.NO \xrightarrow{\text{Oxidation}} (CH_3)_3C.NO_2$$

Tertiary butylamine — Tertiary nitroso-butane — Tertiary nitro-butane.

The majority of them give Liebermann's nitroso reaction (see p. 171).

Isomerism of nitroso-compounds.—It has been shown that aliphatic nitroso-compounds exhibit dynamic isomerism (p. 64) as expressed in the formulæ [1]



Thus the blue monochloro-nitroso-ethane readily changes into the isomeric oxime on standing at the ordinary temperature in ethereal solution.

II.—NITRO-COMPOUNDS [2]

Nitro-derivatives of the hydrocarbons are those in which hydrogen has been replaced by the monovalent nitro group —NO_2. In all of these nitrogen is united directly to carbon, whereas in the isomeric nitrous acid esters (p. 158) it is linked indirectly through oxygen to the alkyl group.

$H_3C.NO_2$ — Nitromethane. $\qquad$ $H_3C.O.N:O$ — Methyl nitrite.

This difference of constitution may be deduced more particularly from the following two reactions :—

1. On reduction nitro-compounds are converted into amino-compounds. Under the same conditions nitrous esters yield an alcohol and ammonia.

$$H_3C.NO_2 + 6H = H_3C.NH_2 + 2H_2O$$

Nitromethane — Methylamine.

$$H_3C.O.NO + 6H = H_3C.OH + NH_3 + H_2O$$

Methyl nitrite — Methyl alcohol.

2. Nitro-derivatives of the hydrocarbons are not decomposed by the action of alkalis ; nitrous acid esters, on the other hand, are hydrolysed to give an alkali nitrite and the corresponding alcohol.

Nitro-compounds are prepared by the interaction of silver nitrite and an alkyl iodide (V. Meyer),

$$C_2H_5I + AgNO_2 = C_2H_5.NO_2 + AgI$$

the corresponding alkyl nitrites being formed at the same time. Since the isomers differ considerably in boiling-point they may be separated

[1] J. Schmidt, *Ber.*, 1902, **35**, 2325. Piloty and Steinbock, *Ber.*, 1902, **35**, 3104. See also Bamberger, *Ber.*, 1903, **36**, 57, 347. [2] It should be noted that certain nitric acid esters prepared on a technical scale, such as nitro-glycerine and nitro-cellulose, are also frequently but incorrectly termed nitro-compounds.

by fractional distillation. Mercurous nitrite can be substituted for silver nitrite in the above reaction.

Nitro-paraffins are frequently prepared from the α-halogen-substituted fatty acids. On treatment with sodium nitrite these yield α-nitro-substituted fatty acids, which readily lose carbon dioxide to give nitro-paraffins. In this manner nitromethane may be obtained from chloracetic acid and sodium nitrite :

$$Cl.CH_2COOH + NaNO_2 = NO_2.CH_2COOH + NaCl$$
$$NO_2.CH_2COOH = CH_3.NO_2 + CO_2$$

In many cases it is also possible to prepare nitro-paraffins by heating the parent hydrocarbon with dilute nitric acid.[1]

In addition to those already mentioned above, the following *properties and reactions of the nitro-paraffins* are of importance. They are colourless, pleasant-smelling liquids, sparingly soluble in water, which distil without decomposition and boil at a much higher temperature than the corresponding isomeric esters of nitrous acid.

Those nitro-compounds in which at least one hydrogen atom is attached to the carbon atom binding the nitro group, *i.e., primary or secondary nitro-compounds, are acidic in character.*

$H_3C.CH_2.NO_2$	$(H_3C)_2CH.NO_2$	$(H_3C)_3C.NO_2$
Nitro-ethane (primary)	2-Methyl-2-nitro-ethane (secondary)	Tertiary nitro-butane.

In such compounds one of the hydrogen atoms in the α-position can be replaced by sodium or potassium. The sodium derivatives are obtained by mixing the nitro-compounds with sodium ethoxide or methoxide in alcoholic solution, salt-formation being accompanied by the simultaneous or preliminary rearrangement of the $—NO_2$ group into $=NO.OH$.[2]

$$H_3C.CH_2.NO_2 + NaOC_2H_5 \longrightarrow H_3C.CH : NO.ONa + C_2H_5.OH$$

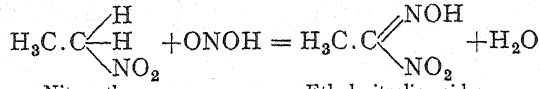
The salts are therefore not derived from nitro-paraffins but from labile isomerides known as **isonitro-paraffins.** Following a suggestion of Hantzsch,[3] the latter are distinguished as the *aci*-**forms** and the true nitro-compounds as **pseudo-acids.** When the solution of an alkali salt of an *aci*-nitro-paraffin is acidified, the labile *aci*-nitro-paraffin which is first liberated changes rapidly in most cases into the nitro-paraffin.

From phenyl-nitro-methane, however, Hantzsch [4] was able to isolate both isomeric forms. The true *phenyl-nitro-methane*, $C_6H_5.CH_2.NO_2$, is stable in the free state, neutral and a non-conductor of electricity. It does not form salts directly, but under the influence of alkalis is converted into aci-*phenyl-nitro-methane*, $C_6H_5.CH : NO.OH$, which although labile in the free state yields stable metallic salts of the type of $C_6H_5.CH : NO.OK$. The *aci*-compound is acid, a conductor of electricity and even in the solid form changes slowly into true phenyl-nitro-methane.

[1] Markownikoff, *Ber.*, 1900, **33**, 1905. Zaloziecki and Frasch, *Ber.*, 1902, **35**, 386.
[2] This change has also been confirmed by optical measurements, *cf.* Hedley, *Ber.*, 1908, **41**, 1195. [3] *Ber.*, 1905, **38**, 1001. [4] Hantzsch and Schultze, *Ber.*, 1896, **29**, 699, 2251.

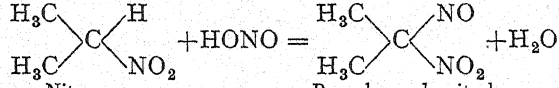
The *behaviour of the nitro-paraffins towards nitrous acid* is very characteristic, and differs according as the compound is primary, secondary or tertiary. It thus serves as a means of distinguishing between these three types.

With a primary nitro-compound a **nitrolic acid** [1] is obtained, which dissolves in alkalis forming a metallic derivative and giving a blood-red coloration.



Nitro-ethane — Ethyl-nitrolic acid (Nitroacetaldoxime).

Secondary nitro-paraffins yield **pseudo-nitrols**, which are to be regarded as nitro-nitroso-compounds. They exist accordingly in two



Nitro-propane — Propyl-pseudo-nitrol.

modifications (see p. 163), are colourless in the solid state and on fusion or in solution develop an intense blue colour.[2]

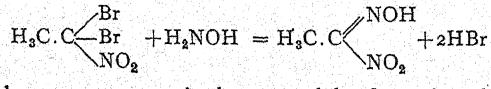
Tertiary nitro-compounds do not interact with nitrous acid at all.

Since alcohols are readily converted into iodides, and these by means of silver nitrite into nitro-paraffins, it is possible by examining the behaviour of the latter towards nitrous acid to distinguish between primary, secondary and tertiary alcohols.

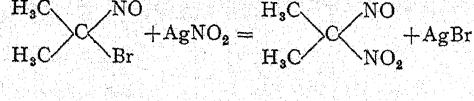
The reaction is carried out by adding sodium nitrite followed by dilute acid to the alkaline solution of the nitro-compound: the solution is then made alkaline and note taken as to the development of a red coloration (nitrolic acid), a blue coloration (pseudo-nitrol) or the absence of any colour change (tertiary nitro-compound). The pseudo-nitrol frequently separates in the solid form, in which case the blue colour is developed on bringing it into solution in chloroform or ether.

On *treatment with bromine or chlorine* in the presence of alkali, primary and secondary nitro-paraffins yield halogen substitution products, in which halogen is attached to the same carbon atom as the nitro group. Tertiary nitro-compounds give no chlorine or bromine derivatives under these conditions.

[1] The constitution of **nitrolic acids** is shown by their formation from dibromo-nitro-paraffins and hydroxylamine.



[2] **Pseudo-nitrols** are more conveniently prepared by the action of nitrogen peroxide on ketoximes (Scholl, *Ber.*, 1888, **21**, 507. J. Schmidt, *Ber.*, 1900, **33**, 872). Their constitution has been proved beyond doubt by their synthesis from bromo-nitroso-hydrocarbons by the action of silver nitrite (Piloty and Stock, *Ber.*, 1902, **35**, 3093).

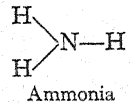


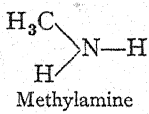
Zinc alkyls and *organo-magnesium compounds* react with nitro-paraffins to form derivatives of hydroxylamine.[1]

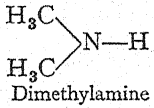
The simple **nitro-olefins** have been less investigated. A typical representative of this class, *nitro-ethylene*, $CH_2:CH.NO_2$, may be obtained by removing the elements of water from β-nitro-ethyl alcohol, $CH_2(OH).CH_2.NO_2$, by means of P_2O_5 or sodium hydrogen sulphate.[2] It is a mobile liquid, b.p. 98·5°, with scarcely a trace of colour. Its most striking property is the powerful irritant effect it has on the mucous membrane of the eyes and respiratory organs. The marked physiological and chemical similarity existing between nitro-compounds and the aldehydes and ketones led to a comparison of nitro-ethylene with acrolein, $CH_2:CH.CHO$, and thus to some understanding of its irritant action. Nitro-ethylene also shares with acrolein a strong tendency to polymerisation, *e.g.* when treated with alkali it polymerises with almost explosive violence.

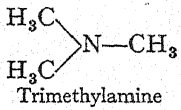
III.—AMINES

The hydrogen atoms of ammonia may be successively exchanged for alkyl groups with the formation of compounds known as amines or amine bases. According as one, two or three hydrogen atoms are replaced the resulting derivatives are described as *primary*, *secondary* or *tertiary amines* respectively.


Ammonia


Methylamine (primary amine)


Dimethylamine (secondary amine)


Trimethylamine (tertiary amine)

All three classes of amines resemble ammonia in possessing basic properties, and like the latter combine directly with acids to form salts in which the originally trivalent nitrogen changes into the pentavalent state. Tertiary amines also combine with alkyl halides to form quaternary ammonium salts, which may be regarded as ammonium halides in which all four hydrogen atoms are displaced by alkyl groups. Corresponding to these salts are the *quaternary ammonium hydroxides* of strongly basic character, closely approximating to potassium and sodium hydroxides in their behaviour.

H_4NCl	$(H_3C)_3NHCl$	$(H_3C)_4NCl$	$(H_3C)_4NOH$
Ammonium chloride	Trimethyl ammonium chloride, or trimethyl-amine hydrochloride	Tetramethyl ammonium chloride	Tetramethyl ammonium hydroxide (a quaternary base)

Quaternary ammonium compounds.

As will readily be understood, the amines present various possibilities of isomerism. We may meet with metamerism due to homology of the alkyl groups attached to the nitrogen atom, as in the case of trimethyl-amine, $(CH_3)_3N$, methyl-ethyl-amine, $(CH_3)(C_2H_5)NH$, and propyl-

[1] Moureu, *C. r.*, 1901, **132**, 837. Bewad, *Ber.*, 1907, **40**, 3065. [2] Wieland and Sakellarios, *Ber.*, 1919, **52**, 898. For phenyl nitro-ethylene see Meisenheimer, *Ann.*, 1907, **355**, 260.

amine, $C_3H_7NH_2$; with chain isomerism, dependent on the different mode of linking of the carbon atoms in the alkyl groups, and which may therefore appear in the case of a single group of three carbon atoms, *e.g.* propyl-amine, $CH_3.CH_2.CH_2.NH_2$, and isopropyl-amine, $(CH_3)_2CH.NH_2$; and finally, if alkyl groups containing a greater number of carbon atoms are present, with position isomerism caused by the varying position of the nitrogen in one and the same carbon chain.

Formation of Amines

I. *Alkylation Methods.*—It was discovered by Hofmann that the hydrogen of ammonia is readily replaced by alkyl groups when an aqueous or alcoholic solution of ammonia is heated with *alkyl halides*. An atom of halogen first unites with a hydrogen atom of ammonia to form hydrogen halide, the place of the hydrogen being then taken by the alkyl residue. In this way one molecule of primary amine and one molecule of hydrogen halide are produced which combine to form the amine salt. (X stands for chlorine, bromine or iodine.)

1. $C_nH_{2n+1}.X+NH_3 = C_nH_{2n+1}.NH_2, HX$

The alkyl halide next reacts with the primary amine, with the formation of a secondary amine.

2. $C_nH_{2n+1}.X+C_nH_{2n+1}.NH_2 = (C_nH_{2n+1})_2NH, HX$

which in a similar manner gives rise to a tertiary amine.

3. $C_nH_{2n+1}.X+(C_nH_{2n+1})_2.NH = (C_nH_{2n+1})_3N, HX$

Finally the latter combines with more alkyl halide to form a quaternary ammonium salt.

4. $C_nH_{2n+1}.X+(C_nH_{2n+1})_3N = (C_nH_{2n+1})_4NX$

These four stages usually proceed simultaneously and lead to the formation of a mixture of all four products. The ease with which the reaction occurs varies with the alkyl halide employed. Owing to greater convenience of manipulation, alkyl iodides are commonly used in the laboratory, whereas on the technical scale the cheaper alkyl bromides are preferred.

In most cases the separation of the mixture of amino-compounds thus obtained is a difficult problem, the quaternary salt being the only product readily isolated. Unlike the salts of primary, secondary and tertiary amines, the quaternary compounds are not decomposed by alkali. When, therefore, a solution containing the four types of salts is treated with potassium hydroxide and distilled, the volatile amines collect in the distillate, leaving the quaternary compound behind in the distilling vessel. The separation of the volatile amines may occasionally be effected by fractional distillation, but more generally one of the chemical methods described later must be employed.

A convenient methylating agent, particularly for primary and secondary amines, has been found in *dimethyl sulphate*.[1]

Another means of methylating primary and secondary amines is to heat them in acid solution with *formaldehyde*. This reaction can also

[1] F. Ullmann, *Ber.*, 1900, **33**, 2476. *Ann.*, 1903, **327**, 104.

be applied to ammonia and ammonium salts. The hydrogen atoms are thus successively replaced by methyl groups, three molecules of formaldehyde being required for the displacement of each two atoms of hydrogen.[1]

$$2NH_3+3H.CHO = 2H_2N.CH_3+CO_2+H_2O$$
$$2NH_3+6H.CHO = 2HN(CH_3)_2+2CO_2+2H_2O$$
$$2NH_3+9H.CHO = 2N(CH_3)_3+3CO_2+3H_2O$$

The formaldehyde is generally introduced in the form of the 40 per cent. solution of commerce, and the reaction provides a simple and economical method of methylation capable of extensive application.

Another method depends on the interaction between alcohols and ammonia under the catalytic influence of certain metallic oxides.[2] When the vapour of ethyl alcohol mixed with ammonia is led over thoria or blue oxide of tungsten at 360°, ethylamine is obtained, together with di- and tri-ethylamines.

$$R.CH_2OH+NH_3 = R.CH_2.NH_2+H_2O$$

II. *Primary amines free from admixed secondary and tertiary derivatives* are formed :—

(*a*) By the reduction of either nitro- or nitroso-paraffins (p. 163), when alkyl-hydroxylamines are produced as intermediate products.[3]

$$\underset{\text{Nitromethane}}{H_3C.NO_2} \longrightarrow \underset{\beta\text{-Methyl-hydroxylamine}}{H_3C.NH.OH} \longrightarrow \underset{\text{Methylamine.}}{H_3C.NH_2}$$

(*b*) By the reduction of nitriles or alkyl cyanides, for example by use of sodium and alcohol (*Mendius reaction*).

$$\underset{\text{Acetonitrile}}{H_3C.CN}+4H = \underset{\text{Ethylamine.}}{H_3C.CH_2.NH_2}$$

(*c*) By boiling esters of isocyanic acid with caustic potash.

$$\underset{\text{Methyl isocyanate.}}{O:C:NCH_3}+2KOH = K_2CO_3+H_2N.CH_3$$

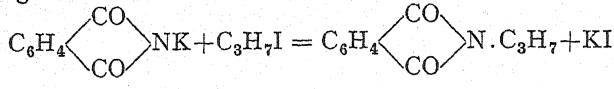
(*d*) By the *Hofmann method*, in which bromine and potassium hydroxide are brought into reaction with acid amides. The amine formed in this case contains one carbon atom less than the amide employed. Acetamide, CH_3CONH_2, for example, yields methylamine, $CH_3.NH_2$. This reaction probably involves the conversion of acetbromamide by loss of HBr into methyl isocyanate, $CH_3.NCO$ (rearrangement). The latter then undergoes the normal decomposition with alkali to form amine and carbon dioxide.

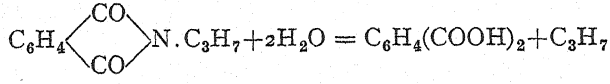
$$CH_3.CO.NH_2+Br_2+KOH = \underset{\text{Acetbromamide.}}{CH_3.CO.NHBr}+KBr+H_2O$$
$$CH_3.CO.NHBr+3KOH = CH_3.NH_2+KBr+K_2CO_3+H_2O$$

(*e*) By *Gabriel's method*, using potassium phthalimide (see p. 455). This aromatic compound reacts with an alkyl halide to form an N-alkyl

[1] Eschweiler, *Ber.*, 1905, **38**, 880. [2] Sabatier and Mailhe, *C. r.*, 1909, **148**, 898.
[3] Primary amines are also obtained by reducing the oximes and hydrazones of aldehydes and ketones.

phthalimide, which on hydrolysis with hot concentrated hydrochloric acid breaks down into phthalic acid and a primary amine. The simultaneous formation of primary, secondary and tertiary amines occurring with free ammonia is here avoided by using as starting material an acid imide, $C_6H_4(CO)_2NH$, containing only *one* hydrogen atom attached to nitrogen, *e.g.*





(*f*) By shaking a carboxylic acid dissolved in concentrated sulphuric acid with a solution of hydrazoic acid in chloroform.

$$R.COOH+N_3H = R.NH_2+CO_2+N_2$$

III. Amines are formed in living organisms by the degradation of amino-acids by elimination of CO_2, or by loss of formic acid and subsequent reduction. Bacteria thus convert α-amino-isovaleric acid into isobutyl-amine.[1] Similarly, the important compound taurine is formed in animal organisms from cysteine (p. 241).

Properties and Chemical Behaviour.—As has been mentioned above, the amines strongly resemble ammonia in their power of forming salts and in many other properties. The lowest members are gases, readily soluble in water and possessing an ammoniacal odour. Unlike ammonia they are combustible. The higher amines are liquids which also dissolve in water, although the solubility diminishes with increase in molecular weight. Like ammonia the amines form double salts with the chlorides of certain metals, chief among which are gold and platinum (p. 10); the composition of these compounds corresponds in most cases to that of the analogous derivatives of ammonia, *e.g.*,

$[NH_3HCl]AuCl_3$ $\quad$ $[N(CH_3)_3HCl]AuCl_3$
$[NH_3HCl]_2PtCl_4$ $\quad$ $[N(CH_3)_3HCl]_2PtCl_4$

Tertiary amines also yield addition products with halogens.[2]

For the behaviour of aliphatic amines on oxidation, see p. 163, also Vorländer, *Ann.*, 1906, **345**, 241.

Complex amino-compounds are produced in small amounts in the human body. Some of these play an important part as "hormones" in the initiation and regulation of biological processes (see hormones).

Conversion of Amines into Alcohols by Means of Yeast and Moulds.[3]—Many yeasts attack primary amines and utilise them for building up their own proteins. The assimilation proceeds in a manner similar to that of the amino-acids, in that ammonia alone is split off and converted by the yeast into protein, while the hydrocarbon residue of the amine retains its identity and is found in the form of the corresponding alcohol

[1] C. Neuberg and Karczag, *Biochem. Z.*, 1909, **18**, 434. [2] Hantzsch and Graf, *Ber.*, 1905, **38**, 2154. [3] Ehrlich and Pistschimuka, *Ber.*, 1912, **45**, 1006.

in the fermented solution. The result of the reaction may be expressed by the equation :

$$R.CH_2.NH_2+H_2O = R.CH_2.OH+NH_3$$

Various moulds also have the power of growing in the presence of amines, and of transforming them into alcohols.

Among the many reactions by which we may distinguish between primary, secondary and tertiary amines, the following may be noted.

1. *Behaviour towards Nitrous Acid.*—Primary amines react with nitrous acid to yield the corresponding primary alcohols, with evolution of nitrogen.[1]

$$CH_3.NH_2+ONOH = CH_3.OH+N_2+H_2O$$

The mechanism of the process is not yet understood. Although only one molecular proportion is indicated in the equation, experiment has shown that the amine nitrite first formed only decomposes in the presence of excess of nitrous acid, the velocity varying as the product $[CH_3.NH_3][NO_2'][HNO_2]$. The reaction is therefore not a simple decomposition of the amine nitrite.[2]

Secondary amines yield nitrosamines.

$$(CH_3)_2NH+HONO = (CH_3)_2N.NO+H_2O$$

This reaction is carried out by treating a concentrated aqueous solution of amine hydrochloride with a concentrated solution of potassium nitrite. The nitrosamine, which separates as an oil, may be extracted with ether and purified by distillation with steam.

Nitrosamines are yellow or yellow-red neutral oils of aromatic smell. From them the secondary bases may be regenerated by treatment with strong reducing agents or by boiling with concentrated hydrochloric acid. Nitrosamines are often of great value in the recognition and purification of secondary amines. When warmed with phenol and concentrated sulphuric acid, and then diluted with water and made alkaline with sodium hydroxide, they give an intense blue or violet coloration (*Liebermann's reaction*).[3] This colour reaction is characteristic of all nitrosamines and many other nitroso-derivatives (see p. 163).

Tertiary aliphatic amines either fail to react with nitrous acid or undergo decomposition.

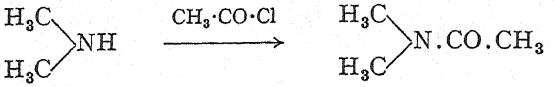
The above reaction may also be employed for separating secondary and tertiary amines from mixtures containing the primary compound, but in this case the latter is always destroyed.

2. *Behaviour on Alkylation.*—As will be seen from the details given on p. 168, it is possible to distinguish between primary, secondary and tertiary amines by treating them with methyl iodide until the whole of the replaceable hydrogen has been displaced by methyl groups. By analysis of the base before and after treatment we may determine how many methyl groups have entered the molecule, and thus classify the original amine.

[1] For abnormalities which may occur during this reaction see *Ber.*, 1876, **9**, 535, and 1877, **10**, 132. [2] T. W. J. Taylor and L. Slater Price, *J. C. S.*, 1928, 1099; 1929, 2052. [3] The colour is due to the formation of an indophenol (Decker and Solonina, *Ber.*, 1902, **35**, 3217); see p. 435.

This reaction is frequently employed in investigating the constitution of alkaloids.

3. *Behaviour towards acid chlorides*, such as benzene sulphonic chloride. Primary and secondary amines interact with acid chlorides and anhydrides, an acyl group (*e.g.* CH_3CO) being substituted for the replaceable hydrogen of the base. Tertiary amines do not react.



In general it is only possible to replace one of the two typical hydrogen atoms in a primary amine by means of acetylating agents, although diacetylation may occur in certain cases.[1]

The acetyl and benzoyl derivatives are usually solid compounds of definite melting-point and are much used for the identification of amines.

On the other hand, with the aid of benzene sulphonic chloride primary, secondary and tertiary amines may be distinguished and isolated from one another. The separation depends on the fact that primary amines react with benzene sulphonic chloride to form derivatives of the type $C_6H_5SO_2.NHR$, which readily dissolve in aqueous alkali, the hydrogen atom attached to nitrogen being replaceable by metals. Secondary amines on the contrary yield compounds of the type $C_6H_5SO_2.NR_2$, which are insoluble in alkali. Tertiary amines do not react at all. In some cases this method requires modification (Hinsberg [2]).

Other reactions of primary amines are as follows: (1) With chloroform and alcoholic potash they yield isocyanides (p. 133). (2) With concentrated nitric acid they are converted into nitramines.

$$\underset{\text{Ethylamine}}{C_2H_5NH_2}+HNO_3 = \underset{\text{Ethyl nitramine.}}{C_2H_5NH.NO_2}+H_2O$$

The latter are solid compounds of weakly acidic nature, in which the hydrogen atom attached to nitrogen is replaceable by metals. (3) Primary amines also unite readily with aldehydes, with elimination of water.

$$CH_3.NH_2+OCH.CH_3 = CH_3.N:CH.CH_3+H_2O$$

Methylamine, $CH_3.NH_2$, is found in *mercurialis perennis* and is prepared by Hofmann's method (p. 169) from acetamide, bromine and caustic soda. It is a colourless gas with a smell resembling that of ammonia; it burns with a yellow flame and is very soluble in water.

Dimethylamine, $(CH_3)_2NH$, occurs in herring brine and is best obtained from nitroso-dimethyl-aniline by heating with caustic soda. It boils at 7°, and is a colourless liquid of ammoniacal smell.

Trimethylamine, $(CH_3)_3N$, occurs in nature in many plants, and also in herring brine. It is a liquid of boiling-point 3·5°, readily soluble in water. On the large scale it is prepared by the distillation of beet molasses or from herring brine. It is conveniently obtained in the pure state by heating ammonium chloride with formaldehyde.

[1] *Ber.*, 1893, **26**, 2853; 1894, **27**, 93; 1901, **34**, 665. [2] Hinsberg, *Ber.*, 1905, **38**, 906; *C.*, 1906, **11**, 15. Vorländer and Nolte, *Ber.*, 1913, **46**, 3212.

The salts of these amines are almost without exception readily soluble in water and alcohol.

Tetramethyl-ammonium iodide, $(CH_3)_4NI$, is a white, crystalline substance which is very sparingly soluble in alcohol. On treatment with moist silver oxide it yields tetramethyl-ammonium hydroxide, $(CH_3)_4NOH$, a white, deliquescent, crystalline compound of strong basic

$$(CH_3)_4NI + AgOH = (CH_3)_4NOH + AgI$$

properties. When strongly heated, this decomposes into trimethylamine and methyl alcohol.

$$(CH_3)_4NOH = (CH_3)_3N + CH_3.OH$$

The more complex ammonium bases break up under the influence of heat to give water, a tertiary amine and a hydrocarbon C_nH_{2n}.

$$\underset{\text{Tetraethyl-ammonium hydroxide}}{(C_2H_5)_4N.OH} = \underset{\text{Triethylamine}}{(C_2H_5)_3N} + \underset{\text{Ethylene.}}{C_2H_4} + H_2O$$

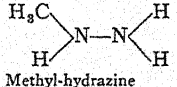
In the case of mixed amines the course of the decomposition is governed by a tendency on the one hand to split off the relatively mobile, loosely bound groups (these include the comparatively small radicals, together with allyl and benzyl), and on the other by the elimination of water to produce olefins of the highest possible degree of symmetry.[1]

By applying this reaction to cyclic amines much valuable information has been gained as to the structure of alkaloids. The study of quaternary ammonium salts has also led to considerable advances in the stereochemistry of pentavalent nitrogen.

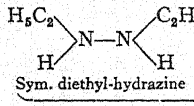
Tetraethyl-ammonium, $N(C_2H_5)_4$, separates at the cathode as the free radical when a solution of tetraethyl-ammonium chloride (or iodide) in liquid ammonia is electrolysed.[2] The blue solution first obtained gradually changes into a colourless one having the same properties. The colourless form is also produced when tetraethyl-ammonium chloride in liquid ammonia is treated with metallic potassium, $K + Cl.NEt_4 = KCl + NEt_4$. The reactions of tetraethyl-ammonium are those of the alkali metals, and it may therefore be described as a *pseudo-metal.*

IV.—ALKYL-HYDRAZINES AND ALKYL-HYDROXYLAMINES

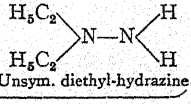
Alkyl-hydrazines :—As in the case of ammonia, the hydrogen atoms in hydrazine, $NH_2—NH_2$, may be substituted by alkyl groups. Alkyl-hydrazines,[3] however, are of little importance and need only be described briefly. On the other hand, phenyl-hydrazine (see aromatic section) is a valuable reagent. A distinction is made between primary and secondary hydrazines, the latter being again divided into those of symmetrical and unsymmetrical structure, as illustrated in the following formulæ :—



Methyl-hydrazine (primary)



Sym. diethyl-hydrazine



Unsym. diethyl-hydrazine

(secondary hydrazines).

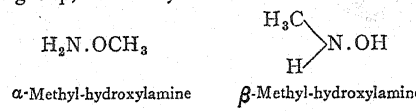
[1] Braun, *Ann.*, 1911, **382**, 1 ; **386**, 273. [2] Schlubach, *Ber.*, 1921, 54, 2811 ; 1923, 56, 1889. [3] See Wieland : *Die Hydrazine.* (Edited by J. Schmidt : Enke, Stuttgart, 1913.)

Among other methods they are obtained by the direct alkylation of hydrazine, and by the reduction of nitrosamines (p. 171).

$$(CH_3)_2N{-}NO \longrightarrow (CH_3)_2N{-}NH_2$$

For the most part they are liquid bases possessing many properties in common with the amines, but differing from them in being powerful reducing agents. With Fehling's solution, for example, they give a precipitate of cuprous oxide in the cold.

Alkyl-hydroxylamines :—By the substitution of a hydrogen atom in hydroxylamine, $NH_2.OH$, by an alkyl group, there may be derived two series of isomeric compounds, *e.g.*



α-Methyl-hydroxylamine β-Methyl-hydroxylamine.

The β-compounds are also formed as intermediate products during the reduction of nitro- and nitroso-compounds.

Aliphatic Diazo-compounds, Diazenes

These are derived from hydrocarbons by inserting two nitrogen atoms in place of two hydrogen atoms attached to the same carbon. The simplest representative is **diazomethane**, CH_2N_2, a yellow, odourless and extremely poisonous gas. It dissolves in anhydrous ether, giving a yellow solution, and is frequently employed in this form as a methylating agent. Diazomethane is prepared by warming nitroso-methyl-urethane with methyl alcoholic potash, the reaction taking the following course :

$$\underset{\text{Nitroso-methyl-urethane.}}{CH_3.\overset{\displaystyle COOC_2H_5}{\overset{|}{N}}.NO} \xrightarrow{KOH} \underset{\text{Potassium-methyl-diazotate.}}{CH_3.N:N.OK} \longrightarrow \underset{\text{Diazomethane.}}{CH_2N_2}$$

It is also obtained by treating hydrazine with chloroform and potassium hydroxide.[1]

$$H_2N.NH_2+CHCl_3+3KOH \longrightarrow >C:N.NH_2+3KCl+3H_2O$$
$$>C:N.NH_2 \longrightarrow CH_2N_2$$

Diazomethane readily decomposes with evolution of nitrogen and is a good methylating agent. For this reason it is often used to detect the presence of a labile hydroxyl group in an organic compound by converting it into the stable $.OCH_3$ group. It rapidly and quantitatively converts acids into their methyl esters and phenols (p. 422) into their methyl ethers. Alcohols, under ordinary conditions, do not react with diazomethane.

$$C_6H_5.OH+CH_2N_2 = C_6H_5.OCH_3+N_2$$

It should be noted that aliphatic diazo-compounds differ in their structure from the diazo-compounds of the aromatic series. The molecular structure of diazomethane presents the same difficulty as that of hydrazoic acid (p. 225). It was formerly represented as , but electron diffraction measurements [2] have shown it to contain a linear arrangement of C, N and N. Two suggested formulæ are $H_2C{=}N{\rightleftharpoons}N$ and $H_2C{\leftarrow}N{\equiv}N$ (*cf.* p. 29). These differ only in the distribution of electrons and should correspond to high values of dipole moment, although of opposite signs. Against them is the low dipole moment, about 1·4, actually found for diazomethane. A satisfactory solution has been provided in terms of the theory of resonance or mesomerism, the compound being represented as a resonance hybrid of the two forms. As the real structure is thus intermediate between these extremes, the physical properties are accounted for.

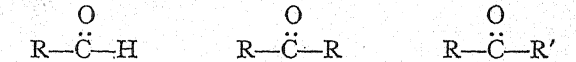
[1] Staudinger and Kupfer, *Ber.*, 1912, **45**, 501. [2] See Sidgwick, *The Organic Chemistry of Nitrogen*, p. 361 (Clarendon Press, 1937).

IX

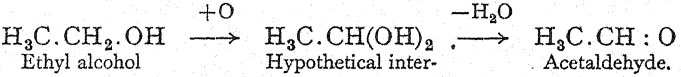
Aldehydes, Ketones and Ketenes

General Formulæ and Nomenclature

Aldehydes and ketones are two important classes of compounds, both of which contain the carbonyl group $>CO$. In aldehydes the group is united on the one hand to a hydrocarbon radical and on the other to hydrogen; in ketones it is combined with two hydrocarbon radicals.

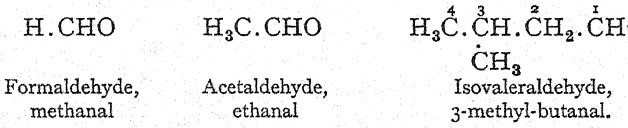


As already indicated on p. 140, **aldehydes** are the first oxidation products of primary alcohols (hence the name aldehyde, from *alcohol dehydrogenatum*). It may be assumed that the first step in this oxidation is the formation of a compound containing two hydroxyl groups attached to a carbon atom. Such derivatives, however, are unstable and generally lose water immediately to form aldehydes. For example:

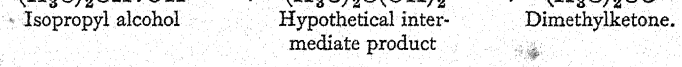


The aldehydes themselves readily undergo further oxidation to yield acids containing the same number of carbon atoms.

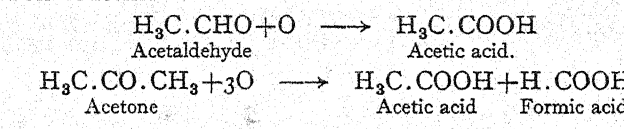
Individual aldehydes take their names from the acids produced from them on oxidation. According to the Geneva nomenclature, the name of an aldehyde is obtained from that of the parent hydrocarbon by the addition of the termination *-al*.



Ketones are oxidation products of secondary alcohols, and their formation may be represented in a similar manner to that of aldehydes.



They are far less readily oxidised than aldehydes, and as they contain no hydrogen atom attached to the carbonyl group it is not possible to obtain from them acids of the same number of carbon atoms. On oxidation they generally decompose with the formation of two acids of lower carbon content.



Ketones generally take their names from the alkyl groups present, but according to the Geneva nomenclature the names are derived from those of the parent hydrocarbons by the addition of the ending *-one*. Polyketones are distinguished as *-diones*, *-triones*, and so on.

$H_3C.CO.CH_3$,	$H_3\overset{1}{C}.\overset{2}{C}O.\overset{3}{C}H_2.\overset{4}{C}H_2.\overset{5}{C}H_3$,	$H_3\overset{1}{C}.\overset{2}{C}O.\overset{3}{C}H_2.\overset{4}{C}O.\overset{5}{C}H_3$
Dimethyl-ketone, propanone	Methyl-propyl-ketone, pentane-2-one	Acetyl-acetone, pentane-2 : 4-dione.

Formation—In addition to the oxidation of alcohols described above, the following reactions also lead to the formation of aldehydes and ketones.

1. Dry distillation of the calcium, barium, thorium or lead [1] salts of carboxylic acids. In this way a ketone is produced containing two similar hydrocarbon radicals. By heating a mixture of the salts of two acids a certain proportion of the unsymmetrical ketone is obtained.

$$\underset{\text{Calcium acetate}}{(H_3C.COO)_2Ca} = CaCO_3 + \underset{\text{Dimethyl-ketone.}}{H_3C.CO.CH_3}$$

$$\underset{\text{Calcium acetate}}{(H_3C.COO)_2Ca} + \underset{\text{Calcium propionate}}{(H_5C_2.COO)_2Ca} = 2CaCO_3 + \underset{\text{Methyl-ethyl-ketone.}}{2H_3C.CO.C_2H_5}$$

If, however, the salt of a fatty acid is heated with an equivalent amount of calcium formate, the product is an aldehyde.

$$\underset{\text{Calcium acetate}}{(H_3C.COO)_2Ca} + \underset{\text{Calcium formate}}{(H.COO)_2Ca} = 2CaCO_3 + \underset{\text{Acetaldehyde.}}{2H_3C.CO.H}$$

2. The above method, involving the use of formates, is limited to the preparation of those aldehydes which distil without decomposition. Since the carboxylic acids are usually readily accessible compounds, many attempts have been made to develop general methods for their conversion into aldehydes. One such method has been found in the catalytic reduction of acid chlorides [2] (*Rosenmund*). For this purpose colloidal solutions of palladium and platinum may be employed as catalysts or, better still, the metals may be used in the finely divided state or precipitated upon some indifferent substance (*e.g.* barium sulphate), in which form they may be separated from the reaction mixture by simple filtration.

Ketones may also be prepared from acids by catalytic methods, the acid or its ester being passed over thorium oxide or aluminium oxide at 300° to 380°.[3] Similarly, when a mixture of an aliphatic acid and formic acid is led in vaporous state over titanium oxide at 300° the formic acid decomposes into water and carbon monoxide, and the latter immediately reduces the aliphatic acid to the aldehyde.[4]

$$R.COOH + H.COOH = CO_2 + H_2O + R.CH : O$$

3. By the action of water on dihalogen derivatives containing the group $—CHCl_2$ or $—CHBr_2$.

$$\underset{\text{Ethylidene chloride}}{H_3C.CHCl_2} + H_2O = \underset{\text{Acetaldehyde.}}{H_3C.CHO} + 2HCl$$

4. Some aldehydes may be prepared from the corresponding nitriles

[1] J. Kenner and F. Morton, *Ber.*, 1939, **72B**, 452. [2] Rosenmund, *Ber.*, 1918, **51**, 585.
[3] Senderens, *C. r.*, 1909, **146**, 1211 ; **148**, 927. [4] Sabatier and Mailhe, *C.*, 1912, **I**, 1290.

by shaking in the cold with a solution of anhydrous stannous chloride and hydrogen chloride in dry ether. The nitrile is stated to combine with HCl to form the imino-chloride, which is then reduced to the aldimine. On treating the mixture with aqueous acids, the aldimine is hydrolysed to aldehyde and ammonia.[1]

$$R.C:N \longrightarrow R.CCl:NH \longrightarrow R.CH:NH \longrightarrow R.CH:O+NH_3$$

5. By certain reactions of the zinc alkyls and organo-magnesium compounds.

Zinc alkyls unite with acid chlorides to give addition products, which by treatment with water yield ketones.

$$C_nH_{2n+1}.C(=O)Cl + Zn(CH_3)_2 = C_nH_{2n+1}.C(OZnCH_3)(CH_3)Cl$$

$$C_nH_{2n+1}.C(OZnCH_3)(CH_3)Cl + H_2O = C_nH_{2n+1}.CO.CH_3 + ZnO + CH_4 + HCl$$

The addition products formed from organo-magnesium halides and nitriles or acid amides also react with water to give ketones.

$$R.CN + IMgR' = \begin{matrix} R \\ R' \end{matrix}\!\!>\!C:N.MgI$$

$$2\begin{matrix} R \\ R' \end{matrix}\!\!>\!C:N.MgI + 4H_2O = 2R.CO.R' + 2NH_3 + MgI_2 + Mg(OH)_2$$

If this reaction could be applied to the simplest nitrile, hydrogen cyanide, it could be used in the preparation of aldehydes. Unfortunately this is not possible. Formamide, the simplest amide, also differs in its behaviour from the higher amides and yields no aldehyde. On the other hand, when formamide is replaced by disubstituted formamides the expected aldehyde is readily obtained.[2]

$$H.CONRR' + R''MgX = HCR''(OMgX)NRR',$$
$$HCR''(OMgX)NRR' + H_2O = R''.CHO + NHRR' + Mg(OH)X$$

Aldehydes, together with secondary alcohols, may be prepared by allowing an excess of formic ester (3 mols.) to interact with organo-magnesium halides (1 mol.). The main reaction may be expressed by the equation [3]

$$R.Mg.Br + H.COOC_2H_5 = Br.Mg.OC_2H_5 + R.CHO$$

6. The action of carbon monoxide on sodium alkyls yields ketones and tertiary alcohols.

7. By treatment with diazomethane, aldehydes are in many cases converted into methyl-ketones.[4]

8. Another useful method of preparing ketones is based on the decomposition of acetoacetic ester and its derivatives by alkalis (see acetoacetic ester).

Reactions of Aldehydes and Ketones

The behaviour of both these classes of compounds on oxidation has already been described.

[1] H. Stephen, *J. C. S.*, 1925, 1874. [2] Bouveault, *C. r.*, 1903, **137**, 987. [3] Gattermann and Maffezzoli, *Ber.*, 1903, **36**, 4152. Tschitschibabin, *Ber.*, 1904, **37**, 850. For additional syntheses of aldehydes by means of the Grignard reaction see Houben, *Ch. Zeit.*, 1905, 667. Bouveault, *C.*, 1905, **I**, 219. [4] F. Schlotterbeck, *Ber.*, 1907, **40**, 479; 1909, **42**, 2559. Arndt and co-workers, *Ber.*, 1928, **61**, 1118, 1949; H. Meerwein and W. Burneleit, *Ber.*, 1928, **61**, 1840.

A number of other reactions common to aldehydes and ketones depend on their power of addition, due to the presence of the carbonyl group. If the double bond in the latter is converted into a single bond a valency is set free on carbon and oxygen, $>C{=}O \rightarrow >\overset{|}{C}\!-\!\overset{|}{O}$. On this basis the following reactions are readily explained.

1. On reduction with sodium amalgam, aldehydes are converted into primary alcohols and ketones into secondary alcohols. In the latter case pinacols (see p. 243) may also be formed as one of the products of reduction.

$$\underset{\text{Acetaldehyde}}{CH_3CHO}+2H = \underset{\text{Ethyl alcohol}}{CH_3CH_2OH}\,; \quad \underset{\text{Acetone}}{CH_3COCH_3}+2H = \underset{\text{Secondary propyl alcohol.}}{CH_3.CH(OH).CH_3}$$

Many ketones can be reduced phytochemically by fermentation with yeast, when the corresponding secondary alcohols are produced.

A more recent method for the reduction of aldehydes and ketones to alcohols is due to Meerwein and Ponndorf.[1] The compounds are heated with an alcoholic solution of aluminium ethoxide (or higher alkoxide), when an equilibrium is set up which may be summarised as $R.CHO+C_2H_5OH \rightleftarrows R.CH_2OH+CH_3.CHO$. By distilling off the volatile acetaldehyde the equilibrium may be so displaced that the alcohol $R.CH_2OH$ can be isolated in good yield. An advantage of the method is that other reducible groups present in the molecule are not affected.

Ketones may be reduced to hydrocarbons by the *Clemmensen* process, using amalgamated zinc and hydrogen chloride.

2. Poly-halogen-substituted aldehydes and ketones unite with water to form hydrates, which are readily dehydrated again at a higher temperature.

$$\underset{\text{Chloral}}{CCl_3.CHO}+H_2O = \underset{\text{Chloral hydrate.}}{CCl_3.CH(OH)_2}$$

$$CCl_3.CO.CH_3+H_2O = CCl_3.C(OH)_2.CH_3$$

Such aldehydes combine even more readily with alcohols to give alcoholates.

$$CCl_3.CHO+C_2H_5OH = CCl_3.CH\!\begin{cases}OH\\OC_2H_5\end{cases}$$

When heated with excess of alcohol, particularly in the presence of dehydrating agents, aldehydes and their alcoholates yield *acetals*. These may be regarded as dialkyl ethers of the (sometimes unknown) hydrate. Acetals are relatively stable towards alkalis but are readily hydrolysed by hot dilute acids.

$$\underset{\text{Acetaldehyde}}{CH_3.CHO}+2C_2H_5OH = \underset{\text{Acetal.}}{CH_3.CH(OC_2H_5)_2}+H_2O$$

Ketones form no alcoholates and only under special conditions acetals.

3. Aldehydes and ketones unite with sodium bisulphite to give crystalline addition compounds, by means of which they may be purified.

[1] Meerwein and Schmidt, *Ann.*, 1925, 444, 221; Ponndorf, *Z. angew. Chem.*, 1926, 39, 138.

On warming these with dilute acids or alkalis the aldehyde or ketone is again set free.

$$CH_3.CHO+NaHSO_3 = CH_3.CH\begin{matrix}OH\\O.SO_2Na\end{matrix}$$

4. Ammonia combines with acetaldehyde according to the equation [1]

$$CH_3.CHO+NH_3 = \underset{\text{Aldehyde-ammonia.}}{C_2H_4ONH_3}$$

but this reaction is not so general as those mentioned above. Formaldehyde, for example, behaves in a different manner. Where simple addition occurs, the reaction is sometimes used with advantage in the purification of the aldehyde. By filtering off the crystalline double compound and warming it with dilute sulphuric acid, the aldehyde is once again set free.

Instead of forming addition compounds with ammonia the ketones yield peculiar condensation products.[2]

5. Both aldehydes and ketones combine with hydrogen cyanide to form cyanhydrins.

$$CH_3.CHO+HCN = CH_3.CH\begin{matrix}OH\\CN\end{matrix}$$

Aldehyde cyanhydrin or nitrile of α-hydroxy-propionic acid.

$$(CH_3)_2CO+HCN = (CH_3)_2C\begin{matrix}OH\\CN\end{matrix}$$

Acetone cyanhydrin.

This reaction, in which a new carbon atom is added to the molecule, is of value in the synthesis of α-hydroxy-acids and α-amino-acids, as will be illustrated later.

Acetone cyanhydrin [3] may be obtained in good yield by adding acetone to a solution of potassium cyanide and allowing sulphuric acid (30 per cent.) to run in slowly with stirring, ice being added to keep the temperature below 20°. The cyanhydrin is then extracted with ether, dried and distilled rapidly. B.p., 81°/15 mm.

Recently cyanhydrins have been used extensively as the starting-point in the preparation of other substances. They may also be prepared by the following reaction.[4] The aldehyde or ketone, or a mixture containing one of these substances, is treated with concentrated sodium bisulphite solution, and the addition product, after separation from impurities, is allowed to interact with potassium cyanide.

$$\begin{matrix}R\\R'\end{matrix}\!\!>\!C\begin{matrix}OH\\SO_3Na\end{matrix} + KCN = \begin{matrix}R\\R'\end{matrix}\!\!>\!C\begin{matrix}OH\\CN\end{matrix} + KNaSO_3$$

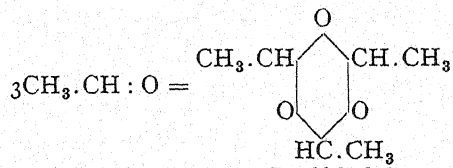
6. Aldehydes and ketones also combine with alkyl magnesium halides, as described on p. 144.

7. Aldehydes have a strong tendency to undergo *polymerisation.*

[1] The molecular formula of aldehyde-ammonia at the ordinary temperature is three times the empirical formula. [2] See Thomae, *C.*, 1905, **II**, 115, 540, 555. [3] K. W. Welch and G. R. Clemo, *J.*, 1928, 2629. [4] Bucherer and Grolée, *Ber.*, 1906, **39**, 1224.

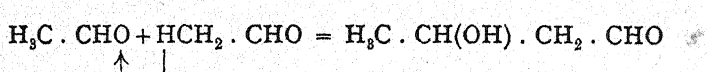
This may take place in two ways, as illustrated in the case of acetaldehyde.

(*a*) When acetaldehyde, b.p. 22°, is mixed with concentrated sulphuric acid, polymerisation occurs with the evolution of much heat and the formation of a compound called *paraldehyde*, b.p. 124°. From vapour density determinations the molecular weight of paraldehyde is found to be three times that of aldehyde. Paraldehyde no longer shows the typical aldehyde reactions but is readily transformed into acetaldehyde by distillation with dilute sulphuric acid. From this it may be concluded that, in the formation of paraldehyde, three molecules of aldehyde combine together in such a manner that the carbon of one molecule always unites with the oxygen of a second.



Acetaldehyde . Paraldehyde [1]

(*b*) Polymerisation of a quite different kind is undergone by aldehydes under the influence of small amounts of dilute alkali. Under these conditions acetaldehyde yields a compound of the same empirical composition but of twice the molecular weight. The new compound contains an open chain of four carbon atoms, as is shown by its behaviour on oxidation, and it cannot be changed back into the original aldehyde by any simple method. In this case two molecules of aldehyde have combined with the simultaneous formation of a new carbon to carbon linking.



Aldol.

Such a union is much more stable than the carbon to oxygen bond in paraldehyde, and polymerisation of this type is often termed *condensation*. The distinction between polymerisation and condensation is, however, somewhat vague, although in general the latter implies the formation of a comparatively stable product. A condensation may occur, not only as in these examples, by direct combination to yield a polymer of the original compound, but the reaction may proceed in other cases with elimination of water, alcohol, ammonia, etc., to form a condensation product which is no longer a polymer of the starting material (see Claisen condensation, p. 256 *et seq.*, and mesitylene from acetone, p. 381). The combination of two or more *different substances* to give a stable product, with or without loss of water, etc., is also frequently described as a condensation.

Combination of this type between two aldehyde molecules is known as the *aldol condensation*.[2] The same reaction may also take place between two different aldehydes, two ketones, or between an aldehyde

[1] For metaldehyde see p. 186. With regard to the polymerisation of other aldehydes, compare Franke and Wozelka, *Monats.*, 1912, **33**, 349. [2] The term aldol is derived from aldehyde-alcohol, the resulting compounds being both aldehydes and alcohols.

and a ketone. The resulting aldehyde alcohols or ketonic alcohols readily split off water and pass into unsaturated aldehydes or ketones, *e.g.*

$$\underset{\text{Aldol}}{CH_3.CH(OH).CH_2.CHO} = \underset{\text{Crotonaldehyde.}}{CH_3.CH{:}CH.CHO} + H_2O$$

Many aldehydes on warming with alkalis are transformed into brown complex resinous products (*aldehyde resins*).

The great reactivity of aldehydes and ketones is by no means limited to the additive reactions illustrated. A large number of other reactions common to both classes depend on their power of exchanging the oxygen of the carbonyl group for other atoms or groups.

Thus, by the action of phosphorus pentachloride, oxygen may be substituted by two atoms of chlorine.

$$CH_3.CHO + PCl_5 = \underset{\text{Ethylidene chloride.}}{CH_3.CHCl_2} + POCl_3$$

Aldehydes and ketones unite with hydrazines to form *hydrazones*, water being eliminated. *Phenyl-hydrazine* may be employed for this purpose,

$$\underset{\text{Phenyl-hydrazine}}{H_3C.CHO + H_2N.NH.C_6H_5} = \underset{\text{Acetaldehyde phenyl-hydrazone.}}{H_3C.CH : N.NH.C_6H_5} + H_2O$$

$$(H_3C)_2CO + H_2N.NH.C_6H_5 = \underset{\text{Acetone phenyl-hydrazone.}}{(H_3C)_2C : N.NH.C_6H_5} + H_2O$$

This reaction, which was first applied to acetaldehyde and benzaldehyde by E. Fischer, is frequently of great service in the isolation and purification of aldehydes and ketones, since the phenyl-hydrazones usually crystallise well, and on heating with hydrochloric acid take up the elements of water to regenerate the original aldehyde or ketone. The phenyl-hydrazone is most readily formed in weak acetic acid solution, and is commonly prepared by use of a mixture of equal volumes of phenyl-hydrazine and 50 per cent. acetic acid, diluted with six volumes of water. If the phenyl-hydrazone has a low melting point it is usually more difficult to purify by crystallisation. For this reason the higher melting *dinitrophenyl-hydrazine*, $(NO_2)_2C_6H_3.NH.NH_2$, is often employed in place of phenyl-hydrazine. *Semicarbazide*, $NH_2.CO.NH.NH_2$, has also proved of value for the isolation and identification of aldehydes and ketones, the *semicarbazones* obtained being in most cases even more readily crystallisable than the corresponding phenyl-hydrazones.[1]

Hydrazones and semicarbazones are converted into hydrocarbons on heating with sodium ethoxide, the reaction taking the following course :

$$>C : N.NH.CONH_2 + H_2O = >C : N.NH_2 + CO_2 + NH_3$$
$$>C : N.NH_2 = >CH_2 + N_2$$

We have here a general method of replacing the oxygen atom of a ketone or aldehyde with hydrogen.[2]

Hydroxylamine, NH_2OH, combines with aldehydes and ketones in the same manner as phenyl-hydrazine, water being split off and the

[1] See Baeyer, *Ber.*, 1894, **27**, 1918 ; 1898, **31**, 2199. [2] L. Wolff, *Ann.*, 1912, **394**, 86.

residue : N.OH taking the place of the oxygen. The resulting compounds are termed *oximes* and are distinguished as aldoximes or ketoximes, according as they are derived from aldehydes or ketones.

$$CH_3CH:O+NH_2OH = CH_3CH:N.OH+H_2O$$
Acetaldoxime.

$$(CH_3)_2C:O+NH_2OH = (CH_3)_2C:N.OH+H_2O$$
Acetoxime.

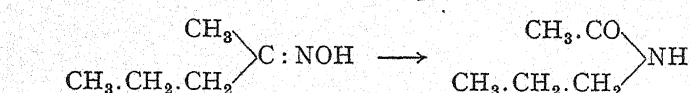
As in the case of the hydrazones, the oximes regenerate the original aldehyde or ketone on being heated with hydrochloric acid. Oximes possess basic as well as acidic properties, forming compounds of the type $CH_3.CH:NOH, HCl$ and $CH_3.CH:NOK$. They usually crystallise well and are also used for the isolation and identification of aldehydes and ketones.

An interesting decomposition of aldoximes, to which reference is made later, is their tendency to break up under certain conditions to form water and a nitrile.

Aldoximes are prepared by treating the aldehyde (1 mol.) with an aqueous solution of hydroxylamine hydrochloride (1 mol.) and sodium carbonate ($\frac{1}{2}$ mol.) in the cold. In the case of aldehydes insoluble in water, an aqueous-alcoholic solution is employed.

The formation of a ketoxime generally occurs less readily. An aqueous or alcoholic solution of the ketone may be treated with the calculated amounts of sodium acetate and hydroxylamine hydrochloride, and heated one to two hours on the water-bath; or an alcoholic solution of the compound may conveniently be sealed up in a tube with hydroxylamine hydrochloride, and heated for eight to ten hours at 160° to 180°. In the latter case, however, intramolecular rearrangement sometimes takes place and the expected oxime is not obtained.

Under the influence of phosphorus pentachloride in ether or benzene (and of other reagents such as benzene-sulphonic chloride, and solutions of hydrochloric or sulphuric acid in glacial acetic acid),[1] the ketoximes undergo molecular rearrangement and are converted into acid amides (*Beckmann rearrangement*). For example,



Methyl-propyl-ketoxime — Acetpropylamide.

Under this treatment stereoisomeric ketoximes yield different products and the Beckmann reaction has therefore been employed as a general means of determining the structure of these compounds. (For further details see p. 57.)

It has already been mentioned (p. 56) that the oximes were one of the first groups of stereoisomeric nitrogen derivatives to be discovered.

On reduction both aldoximes and ketoximes are converted into primary amines.

$$CH_3.CH:NOH+4H = CH_3.CH_2.NH_2+H_2O$$
$$(CH_3)_2C:NOH+4H = (CH_3)_2CH.NH_2+H_2O$$

[1] For a survey of these reactions see A. H. Blatt, *Chem. Reviews*, 1933, **12**, 216.

Detection of Aldehydes

(*a*) As already stated, aldehydes are very easily oxidised, and therefore possess reducing properties by means of which they may be detected. Thus, on treating a moderately dilute solution of an aldehyde with an ammoniacal solution of silver nitrate a more or less brilliant silver mirror is obtained, the formation of which may be hastened by gentle warming. Aliphatic aldehydes differ from those of the aromatic series in rapidly reducing Fehling's solution, with precipitation of red cuprous oxide.

(*b*) A solution of rosaniline hydrochloride which has been decolorised by sulphur dioxide (*Schiff's reagent*) gives an intense reddish-violet colour [1] with aldehydes.

(*c*) An aqueous solution of the sodium salt of nitro-hydroxylaminic acid reacts with a large number of aldehydes to give hydroxamic acids. On subsequent addition of ferric chloride a red coloration is produced. This permits of the detection of very small quantities of an aldehyde.[2]

For the *detection of ketones* by the conversion of ketoximes into bromo-nitroso-compounds, see p. 163 and footnote.

SATURATED ALDEHYDES

Formaldehyde, *methanal*, H.CH : O, is formed by the oxidation of methyl alcohol, *e.g.* when the vapour of methyl alcohol mixed with air is led over heated catalysts such as silver, copper or platinum black. It can also be prepared by oxidising ethylene (preferably diluted with nitrogen or methane) with gaseous oxygen in the presence of catalysts.[3]

Following on the discovery of Butlerow that formaldehyde could be condensed to a sugar, Baeyer suggested that in plants containing chlorophyll the conversion of carbon dioxide into carbohydrate takes place by way of formaldehyde as an intermediate. An important advance was made when Baly, Heilbron and Barker [4] showed that carbon dioxide in aqueous solution containing suspended coloured catalysts (*e.g.* colloidal uranium hydroxide) is converted by ordinary visible light into formaldehyde, and the latter into reducing sugars. Formaldehyde has since been isolated from various plants, but only from tissue containing chlorophyll which had been exposed to light.[5] Hence it appears very probable that formaldehyde is actually an intermediate product in the conversion of carbon dioxide into carbohydrates and other plant products. By means of the aldol condensation (see p. 180) the formaldehyde may then be converted into sugar, starch, cellulose or resinous products.[6] Generally speaking, all life depends on this reduction of carbon dioxide in the chloroplast under the influence of sunlight.

[1] For the nature of these coloured compounds see Wieland and Scheuing, *Ber.*, 1921, **54**, 2527. [2] Baudisch and Coert, *Ber.*, 1912, **45**, 1775. Steinkopf and Jürgens, *J. pr. Ch.* (2), 1911, **84**, 686. [3] Willstätter and Bommer, *Ann.*, 1921, **422**, 36. [4] *J. C. S.*, 1921, **119**, 1025. See, however, G. Mackinney, *J. A. C. S.*, 1932, **54**, 1688; Qureshi and Mohammad, *J. Physical Chem.*, 1932, **36**, 2205. [5] G. Klein and O. Werner, *Biochem. Zeit.*, 1926, **168**, 361. [6] Willstätter, *Ber.*, 1917, **50**, 1777; *Untersuchungen über die Assimilation der Kohlensaüre* (Springer, Berlin, 1918). Willstätter, *Z. ang. Ch.*, 1919, **32**, 329.

Pure formaldehyde is a gas at ordinary temperatures, but condenses under strong cooling to a colourless liquid of b.p. −21°. It possesses a pungent, penetrating smell, and is a powerful disinfectant. It is readily soluble in water and comes on to the market as a 40 per cent. solution, under the name of *formalin*. The latter usually contains from 12 to 18 per cent. of methyl alcohol, which is introduced during the process of manufacture and serves to prevent the formation of a sediment. Formaldehyde is a weakly acidic compound and yields salts with strong bases.

Polymerisation of Formaldehyde

Formaldehyde very readily undergoes polymerisation and the products so formed have been made the subject of extensive investigations by Staudinger.[1] When an aqueous solution of formaldehyde is evaporated, it leaves behind a white solid, *paraformaldehyde*, which melts indefinitely between 120° and 130°. This substance dissolves readily in water, giving a solution possessing the properties of aqueous formaldehyde. On being heated it decomposes to regenerate formaldehyde. Solutions of formaldehyde may also be polymerised by means of chemical reagents such as concentrated sulphuric acid to form *α-polyoxymethylene*, a white solid which melts between 160° and 170°, with decomposition into gaseous formaldehyde. This dissolves slowly in water and is only slowly attacked by boiling aqueous alkali. According to Staudinger there is no essential difference between the above two products, except in their degree of molecular complexity. Both are mixtures formed by the combination of a number of formaldehyde molecules to give long chains of the type

$$\ldots O.CH_2.(O.CH_2)_x.O.CH_2\ldots$$

followed by union with a molecule of water to yield the "dihydrate"

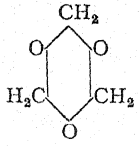
$$HO.CH_2.(O.CH_2)_x.O.CH_2.OH.$$

The paraformaldehydes are regarded as mixtures of **α-polyoxymethylene dihydrates** composed of chains containing about 10 to 50 formaldehyde units. They are thus of relatively low molecular weight, in agreement with their low melting-point and ready solubility in water. The polyoxymethylenes of m.p. 160° to 170° are assumed to be dihydrates with longer chains, of the order of 100 formaldehyde units. Owing to their greater complexity these compounds have a higher melting-point and a lower solubility. With boiling water they pass slowly into solution, forming products of a lower degree of polymerisation. By varying the method of preparation it has been found possible to obtain α-polyoxymethylene dihydrates of any intermediate chain length.

The average molecular weight of the above mixtures cannot be determined by the cryoscopic method, and even the quantitative estimation of the terminal hydroxyl groups only gives very uncertain results. The number of constituent formaldehyde units is therefore deduced by comparing the properties of the compounds with those of other

[1] For references see *Ann. Rep. Chem. Soc.*, 1929, 108, and Staudinger and W. Kern, *Ber.*, 1933, 1863.

polymeric series, in which the molecular complexity can be measured directly. A series of this kind is that of the analogous polymeric *α-polyoxymethylene dimethyl ethers* and *diacetates* prepared by Staudinger. In these cases the molecular weight could be determined cryoscopically and confirmed by analysis, *e.g.* of the content of methoxyl and formaldehyde. Like the dihydrates, the dimethyl ethers form a series of polymerides in which the formaldehyde units vary from a small number up to about 100. The ethers are stable towards hot aqueous alkali, hence it is concluded that the oxygen-carbon linkings of the chains are not disrupted by this reagent. The decomposition of the dihydrates by alkalis must therefore take place through the terminal hydroxyl groups, in the absence of which the molecule is not attacked. This property excludes the alternative cyclic structure for the polyoxymethylenes, in which the formaldehyde units were supposed to unite to give a closed ring such as



Under the influence of strong alkalis, formaldehyde may either undergo the Cannizzaro reaction (p. 440) to give a mixture of formic acid and methyl alcohol, or a polymeride may be produced.[1]

Finally, the formaldehyde molecules may react together in a third manner. When an aqueous solution of formaldehyde is treated with lime water or magnesium hydroxide, six molecules of the aldehyde condense with the production of " formose," a mixture of sugars of the formula $C_6H_{12}O_6$ (see Sugars). It is this ease of polymerisation or condensation which enables formaldehyde to play such an important part in the assimilation of plants.

In addition to its use as a disinfectant, formaldehyde is also employed for the preservation of anatomical preparations, since it possesses the property of transforming proteins into a hard elastic mass, insoluble in water. Further, it is extensively utilised in the preparation of diphenyl-methane derivatives for the manufacture of dye-stuffs, as will be described later.

When treated with ammonia, formaldehyde does not yield an aldehyde ammonia, but gives a complex substance, *hexamethylene tetramine* [2] or *urotropine* $(CH_2)_6N_4$, m.p. 280°, which is employed medicinally as an internal disinfectant, especially for the urinary canal. The disinfectant properties possibly depend on the liberation of formaldehyde.

Osmium brings about a decomposition of formaldehyde into methyl alcohol and carbon dioxide, $3H.CHO+H_2O = CO_2+2CH_3OH$.[3]

Methylal, methylene dimethyl ether, $CH_2(OCH_3)_2$, is frequently used in place of formaldehyde for condensations and is a very good solvent for many organic compounds. It may be prepared by cautious oxidation of methyl alcohol with manganese dioxide and sulphuric acid, or by the action of sodium methoxide on methylene iodide. It is a pleasant-smelling liquid of b.p. 42°.

[1] Mannich, *Ber.*, 1919, **52**, 160. The Cannizzaro reaction is said to be catalysed by nickel powder, see p. 439. [2] For the constitution of hexamethylene tetramine see Duden and Scharff, *Ann.*, **288**, 218. [3] E. Müller, *Ber.*, 1921, **54**, 3214. *Zeit. physik. Chem.*, 1923, **107**, 347.

Formaldehyde condenses with phenols (p. 423) to form a hard resinous product (*bakelite*) which is utilised as an insulating material and for the manufacture of a variety of articles; the products obtained by reaction with phenol- and naphthalene-sulphonic acids are employed as artificial tannins (*neradol*). With casein, formaldehyde yields a tough horny mass used as artificial horn or ivory (*galalith, etc.*).

Formaldehyde-sodium sulphoxylate (*rongalite C, hydraldite*) is a reducing agent employed in vat dyeing. It may be prepared from formaldehyde and sodium hydrosulphite in alkaline solution.

$$H.CHO+NaHSO_2+2H_2O = HC\begin{matrix}H\\OH\\OSONa\end{matrix}, 2H_2O.$$

Acetaldehyde, *ethanal*, $CH_3.CH:O$ generally known as aldehyde, is formed by the methods indicated above, and is prepared by the oxidation of ethyl alcohol with sodium bichromate and sulphuric acid. It is also obtained as a by-product in the manufacture of alcohol (see p. 149). The conversion of acetylene into acetaldehyde under the catalytic influence of mercury salts has been known for many years and is used in the manufacture of acetic acid. Acetaldehyde is a colourless, mobile liquid of peculiarly suffocating smell. It boils at $+21°$, melts at $-121°$, and is readily soluble in water, alcohol and ether. The presence of small amounts of acetaldehyde is best confirmed by condensation with dimethyl-cyclohexanedione.[1]

The most important polymerisations of acetaldehyde have already been described on pp. 180 and 181, but it may be added that it also polymerises under the influence of acids at temperatures below 0° to give *metaldehyde*. The latter forms long, glistening crystals which sublime at 115° without melting, being partially converted into ordinary aldehyde. For a long time metaldehyde was believed to be stereoisomeric with paraldehyde, but later investigation has shown it to be a polymeride [2] and not an isomeride of this compound.

The following derivatives of acetaldehyde are of importance :—

Acetal, $CH_3.CH(OC_2H_5)_2$, b.p. 104°, is formed together with aldehyde by the oxidation of alcohol. It is frequently used in place of aldehyde for condensation reactions.

Trichloro-acetaldehyde, chloral, $CCl_3.CHO$, is obtained when chlorine is led into alcohol, first with cooling and finally at a higher temperature. It is assumed that the first step is the conversion of alcohol into aldehyde, chlorine acting as an oxidising agent, followed by substitution and the production of chloral, which is obtained united with alcohol as the crystalline **chloral alcoholate,** $CCl_3.CHOH.OC_2H_5$. On distillation with concentrated sulphuric acid this yields chloral as an oily liquid, b.p. 97°, possessing a characteristic odour. On treatment with alkali at the ordinary temperature it decomposes into chloroform and formic acid.

$$\begin{matrix}CCl_3.CHO\\H.OK\end{matrix} = CHCl_3+HCOOK$$

[1] D. Vorländer, *Zeit. für ang. Chem.*, 1929, **42**, 46. [2] Hantzsch and Oechslin, *Ber.*, 1907, **40**, 4341.

Chloral hydrate, $CCl_3.CH(OH)_2$, is produced by the action of water on chloral; it forms readily soluble crystals, m.p. 57°, and is used as a soporific. From the theoretical standpoint it is of interest as being one of the few compounds containing two OH groups bound to the same carbon atom.

Lactaldehyde, $CH_3.CHOH.CHO$, crystallises in needles, m.p. 105°.

UNSATURATED ALDEHYDES

Unsaturated aldehydes show on the whole the same chemical reactivity as the saturated compounds, but owing to the presence of multiple bonds they also undergo those additive reactions characteristic of the unsaturated hydrocarbons. They are formed, among other methods, by molecular rearrangement from tertiary acetylenic alcohols.[1]

Acrolein, *propenal,* acrylic aldehyde, $CH_2:CH.CHO$, is prepared by removing the elements of water from glycerol by means of potassium bisulphate or boric acid.[2] In place of the potassium bisulphate commonly employed as catalyst, any sulphate may be used which yields free sulphuric acid at a comparatively low temperature. The highest and purest yields of acrolein are given by passing the vapour of glycerol over heated magnesium sulphate.

$$CH_2(OH).CH(OH).CH_2(OH) = CH_2:CH.CHO + 2H_2O$$

It is a colourless liquid, b.p. 52°, which is difficultly soluble in water and has an extremely unpleasant pungent smell. The tendency of acrolein to polymerise is so great that it usually changes in a short time into a white, flocculent compound called *disacryl.* Acrolein is readily oxidised, even in the air, to form acrylic acid. Catalytic hydrogenation in the presence of nickel at 50° to 60° converts it into *propionaldehyde.*

Crotonaldehyde, $CH_3.CH:CH.CHO$, is produced by heating aldehyde with dil. hydrochloric acid, or with a solution of sodium acetate, aldol being formed as an

$$2CH_3.CHO \longrightarrow CH_3.CH(OH).CH_2.CHO \longrightarrow CH_3.CH:CH.CHO$$

intermediate product. It is a pungent-smelling liquid, b.p. 105°, which on oxidation is transformed into solid crotonic acid.

αβ-Hexenic-aldehyde, $CH_3.CH_2.CH_2.CH:CH.CHO$, is a constituent of green plants and has been isolated from beech leaves[3] as a colourless oil of peculiar smell, b.p. 47° to 48° under 17 mm. pressure.

Citral, geranial, $(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.CHO$, b.p. 226°, is an important unsaturated aldehyde characterised by a pleasant smell. It is closely related to geraniol and occurs in various essential oils. The most convenient source of preparation is lemon-grass oil. On being

[1] H. Rupe and co-workers, *Helv. Chim. Act.*, 1928, **11**, 49. [2] *Ber.*, 1899, **32**, 1352. *Ber.*, 1902, **35**, 1136. *J. pr. Ch.* (2), 1905, **71**, 474. Bergh, *J. pr. Ch.* (2), 1909, **79**, 351. [3] Curtius and Franzen, *Ann.*, 1912, **390**, 89.

heated with aqueous potassium carbonate, citral takes up a molecule of water and decomposes into *methyl-heptenone* and acetaldehyde.

$$(CH_3)_2C:CH.CH_2.CH_2.CO.CH_3 + CH_3.CHO$$
Methyl-heptenone — Acetaldehyde.

Citral occurs in α and β isomerides (*cis* and *trans* forms). When reduced it yields geraniol together with some nerol (p. 155), and both of these alcohols on oxidation are converted into citral. It is used in the manufacture of the perfumes, *α- and β-ionones* (see next page).

KETONES

Acetone, *dimethyl-ketone*, *propanone*, $CH_3.CO.CH_3$, is prepared industrially from raw wood spirit (see p. 196), and by the dry distillation of calcium acetate. In recent years a fermentation process involving the use of *Bacillus macerans* has been developed for the technical preparation of acetone from starch. Acetone occurs in small quantities in blood and normal urine, and in larger quantities in the urine of diabetic patients (*cf.* p. 193). It is a liquid of pleasant smell which boils at 56° and solidifies at −94°. With water, alcohol and ether it is miscible in all proportions. The most important reactions of acetone have already been described on p. 178 *et seq.*, to which reference should be made. Acetoxime forms white prisms, m.p. 69°. With nitrous acid acetone yields *iso-nitroso-acetone*, $CH_3.CO.CH:N.OH$.

Acetone is an excellent solvent for a variety of organic compounds; it enters into the manufacture of smokeless powder and cordite, and forms the starting material in the production of chloroform, bromoform, iodoform and sulphonal.

The condensation of acetone leads to the formation of *unsaturated ketones*.[1] These compounds combine the properties of ketones with those of ethylene. Thus they unite with ozone to form unstable ozonides.

Mesityl oxide, $(CH_3)_2C:CH.CO.CH_3$, a colourless liquid, b.p. 122°, with a smell resembling peppermint and **phorone**, $(CH_3)_2C:CH.CO.CH:C(CH_3)_2$, m.p. 28° and b.p. 196°, are produced together by treating acetone with dehydrating agents such as hydrochloric acid, concentrated sulphuric acid or zinc chloride. More vigorous treatment with concentrated sulphuric acid carries the process further, yielding the aromatic hydrocarbon **mesitylene** (p. 381).

Pseudo-ionone, $C_{13}H_{20}O$, is formed by the condensation of citral with acetone under the influence of baryta water,

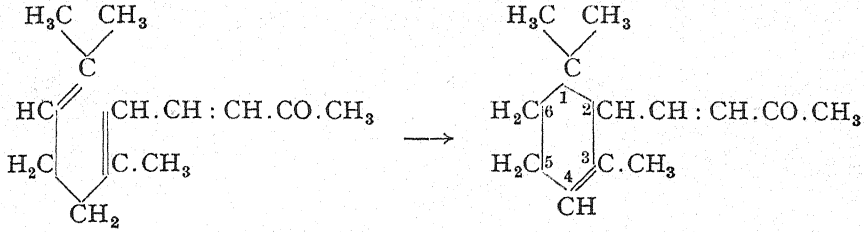
$$(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.CHO + H_2CH.CO.CH_3 \longrightarrow$$
Citral — Acetone.

$$(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.CH:CH.CO.CH_3 + H_2O$$
Pseudo-ionone.

When boiled with dilute sulphuric acid it is readily transformed into a mixture of the isomeric ionones. The latter are reduced benzene

[1] Knoevenagel and co-workers, *Ber.*, 1906, **39**, 3462.

derivatives which occur in two modifications as α- and β-**ionones**, having the double bonds in the ring in the Δ^3 and Δ^2 positions respectively.



Pseudo-ionone α-Ionone.

Related to the ionones is **irone** which possesses the formula $C_{14}H_{22}O$, and is thus a higher homologue [1] of the ionones. The additional methyl group is attached to position 6 of the β-ionone structure. This compound occurs in orrisroot and gives rise to the pleasant perfume of the violet. As ionone strongly resembles irone in smell, it is prepared on a technical scale by the above method, citral or preferably lemon-grass oil being treated with acetone in the presence of an alkali (*e.g.* sodium ethoxide) and the pseudo-ionone so formed converted into ionone by means of sulphuric acid or sodium bisulphate.

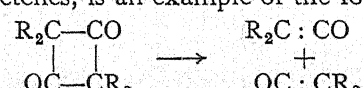
KETENES [2]

The aliphatic series has recently been extended by the addition of a new class of compounds termed ketenes. These include the simple ketene $CH_2:CO$ discovered by Wilsmore, substituted ketenes discovered by Staudinger, who also noted their extraordinary reactivity, and the double ketene of Diels, $O:C:C:C:O$, somewhat inaccurately called carbon suboxide. All these compounds contain tetravalent carbon. The characteristic group of the ketenes is $>C:C:O$, and although they show none of the typical carbonyl reactions, they are here on formal grounds classed with the ketones.

Preparation—The majority of ketenes of the general formula $R_2C:C:O$ have been prepared according to the method of Staudinger by acting on α-halogen-substituted acid chlorides with metals, preferably zinc, in hydroxyl-free solvents. In this manner dimethyl-ketene is obtained from dimethyl-bromacetyl bromide.

$$(CH_3)_2CBr.COBr+Zn = (CH_3)_2C:CO+ZnBr_2$$

In addition, ketenes are also obtained by the disruption of ring compounds and of diazomethane derivatives. The fission of diketocyclobutane derivatives, which are themselves dimolecular polymerisation products of the ketenes, is an example of the former type.



[1] Ruzicka, Seidel and Schinz, *Helv. Chim. Acta*, 1933, **16**, 1143. [2] See *Die Ketene* by H. Staudinger, edited by J. Schmidt (Enke, Stuttgart, 1912). Also Staudinger and co-workers, *Helv. Chim. Acta*, 1918-1924.

The simplest ketene, $CH_2 : CO$, is readily prepared[1] by passing the vapour of acetone at dull red heat through a glass tube filled with broken tile, when ketene and methane are formed.

$$CH_3COCH_3 = H_2C : CO + CH_4$$

Properties and Reactions.—The ketenes, $R_2C : C : O$, belong to the large class of compounds containing two adjacent double bonds in the molecule, and are thus to be grouped with carbon dioxide, $O : C : O$, isocyanates, $RN : C : O$, and mustard oils, $RN : C : S$. With these they possess a number of reactions in common, although differing in their yellow colour. For example, ketenes react with water, alcohols, ammonia, amines and phenyl-hydrazine, when addition occurs at one of the double bonds, leaving the other unattacked, with the formation of acids or their derivatives.

$$R_2C : C : O + HOH = R_2CH.COOH$$
$$R_2C : C : O + HNH_2 = R_2CH.CONH_2$$

In some respects, however, the reactions of the ketenes place them in a class by themselves. Thus they undergo auto-oxidation, and unite with certain tertiary bases such as quinoline and pyridine to form peculiar compounds known as "ketene bases."

Another reaction typical of the ketenes is their power of combining with various unsaturated substances to give addition compounds. This process usually results in the formation of a four-membered ring, one molecule of ketene combining with one molecule of the unsaturated substance :

$$\begin{matrix} R_2C{=}CO \\ + \\ R_1{=}R_2 \end{matrix} \longrightarrow \begin{matrix} R_2C{-}CO \\ | \quad | \\ R_1{-}R_2 \end{matrix}$$

The ease with which many ketenes polymerise may be traced to a similar cause. In this case derivatives of cyclobutane are generally produced.

$$2R_2C{=}CO \longrightarrow \begin{matrix} R_2C{-}CO \\ | \quad | \\ OC{-}CR_2 \end{matrix}$$

Ketene, $CH_2 : CO$ (preparation see above), is a colourless gas with an exceedingly unpleasant, pungent smell, reminiscent of both chlorine and acetic anhydride. Inhalation of the vapour causes severe headache. At $-56°$ it condenses to a colourless liquid which solidifies at $-151°$ to a white crystalline mass. The gas is readily soluble in ether. In the pure state ketene is very unstable and can only be preserved at a low temperature ($-80°$). At room temperature it polymerises slowly, and on strong heating decomposes into ethylene and carbon monoxide.

Methyl-ketene, $(CH_3)CH : CO$, has so far only been obtained in ethereal solution. Even concentrated solutions are colourless, and these, when cooled in liquid air, solidify to a mass of colourless crystals. At a little above $-80°$ it polymerises spontaneously. Solutions of the ketene, even at high dilutions, soon assume a yellow or yellowish-brown colour, probably owing to the formation of polymerisation products.

Dimethyl-ketene, $(CH_3)_2C : CO$, is readily obtained in dilute ethereal or ethyl acetate

[1] Schmidlin and Bergman, *Ber.*, 1910, **43**, 2821. For the original method of preparation see Wilsmore, *J. C. S.*, 1907, **91**, 1938.

solution by the action of zinc on bromo-isobutyryl bromide. The pure ketene is a yellow liquid of unpleasant, choking smell, which boils at 34° to give a pale yellow gas. The solid substance, m.p. −98°, is also yellow in colour. Pure dimethyl-ketene is very unstable and polymerises within a few hours to tetramethyl-diketo-cyclobutane.

THIO-ALDEHYDES AND THIO-KETONES

These compounds are produced by the action of hydrogen sulphide on aldehydes and ketones. They are liquids with a repulsive smell, and readily change by polymerisation into almost odourless compounds known as tri-thio-aldehydes or tri-thio-ketones. On oxidation with potassium permanganate they yield sulphones.

Thio-acetaldehyde, ethan-thial, $CH_3.CH:S$, is a repulsively smelling oil, not known in the pure state, which on treatment with acids is readily converted into *tri-thio-aldehyde*, $(CH_3.CHS)_3$. The latter occurs in two modifications melting at 101° and 125° respectively, both of which are odourless and may be oxidised to give the same *triethylidene trisulphone*, $C_6H_{12}(SO_2)_3$.

Tri-thio-acetone, $[(CH_3)_2CS]_3$, is obtained as the final product of the action of hydrogen sulphide on a mixture of acetone and concentrated hydrochloric acid. It melts at 24°, and on oxidation with permanganate yields *tri-sulphone-acetone*, $[(CH_3)_2C:SO_2]_3$.

X

Monobasic Carboxylic Acids

The characteristic group contained in all these acids is the carboxyl group —C(=O)OH the hydrogen of which can be replaced by metals with the formation of salts. Consequently the basicity of the acids depends on the number of carboxyl groups present in the molecule. Those acids containing one such group are monobasic (monocarboxylic acids), and those possessing two such groups are dibasic (dicarboxylic acids), and so on, as illustrated by the following examples :—

CH_3COOH	$CH_2(COOH)_2$	$C_3H_5(COOH)_3$
Acetic acid	Malonic acid	Tricarballylic acid
(monobasic)	(dibasic)	(tribasic).

The acids are called saturated or unsaturated according to the state of the hydrocarbon radicals attached to the carboxyl group. Monobasic saturated acids of the aliphatic series are commonly known as **fatty acids,** since many of them are prepared from fats.

Nomenclature.—The names of the fatty acids all terminate in the syllable *-ic*, and generally indicate their source of preparation, as in formic acid (from ants), or the number of carbon atoms in the molecule, as in hexoic acid, $C_6H_{12}O_2$.

According to the Geneva nomenclature the acids are named from the parent hydrocarbon by the addition of the word " acid," polybasic acids being further distinguished as di-, tri-, tetra-acids and so on.

The usual English and American practice is to employ the common names in describing saturated monobasic acids and their derivatives,

the position of substituents being shown by the use of numbers or Greek letters (see p. 101). Polybasic acids are frequently described as polycarboxy hydrocarbons, and unsaturated linkings indicated by the endings -ene, -ine (see p. 117), as in the following examples. The Geneva nomenclature is also given in italics.

$CH_3.CH_2.CH(CH_3).COOH$
α-Methyl-butyric acid or methyl-ethyl-acetic acid
(*2-Methyl-butane acid*)

$CH_3.CH:CH.CH_2.CH_2.COOH$
γδ- or Δ^4-hexenic acid
(*4-Hexene-1-acid*)

$HOOC.CH_2.CH_2.CH:CH.COOH$
Δ^{α}-Butene-αδ-dicarboxylic acid
(*2-Hexene-1 : 6-diacid*).

In the discussion of reactions it is frequently necessary to refer to that group of atoms which remains when the hydroxyl group is removed from a fatty acid; such groups, which are not capable of existence in the free state, are known as "acyl" groups or acid radicals, and are named after the corresponding acid by adding the termination *-yl* to a suitable contraction of the latter, *e.g.*

$H.\overset{\overset{\cdot\cdot}{O}}{\overset{\vert}{C}}-$	$H_3C.\overset{\overset{\cdot\cdot}{O}}{\overset{\vert}{C}}-$	$C_2H_5.\overset{\overset{\cdot\cdot}{O}}{\overset{\vert}{C}}-$	$C_3H_7.\overset{\overset{\cdot\cdot}{O}}{\overset{\vert}{C}}-$
Formyl	Acetyl	Propionyl	Butyryl.

I.—SATURATED MONOBASIC FATTY ACIDS, $C_nH_{2n+1}COOH$

Properties and Chemical Behaviour.—The fatty acids of low carbon content are corrosive liquids of pungent smell which distil without decomposition, dissolve readily in water and are acid in reaction. Those next in the series (C_4 to C_9) are oily compounds, sparingly soluble in water, and smelling unpleasantly of rancid butter or perspiration. The members from C_{10} upwards are solids, which are no longer soluble in water but dissolve readily in alcohol and ether; they cannot be distilled without decomposition except under diminished pressure.

As already mentioned, the hydrogen of the carboxyl group is replaceable by metals and also by alkyl groups. In the latter case the esters formed have the same characteristic properties as those of the mineral acids (p. 156).

Acids may also be converted into *acid chlorides* by exchanging the hydroxyl group for chlorine, or into *acid anhydrides* by exchanging the replaceable hydrogen of the carboxyl group by an acid radical,

$$CH_3.CO.Cl + CH_3.CO.ONa = \begin{matrix} CH_3.CO \\ CH_3.CO \end{matrix}\!\!>O + NaCl$$

Acetyl chloride Sodium acetate Acetic anhydride.

On replacing the hydroxyl group by —SH we obtain *thio-acids*, by $-NH_2$ *acid amides*, and from the latter by removal of water the *nitriles*.

$CH_3.CO.SH$	$CH_3.CO.NH_2$	$CH_3.C{\equiv}N$
Thio-acetic acid	Acetamide	Acetonitrile.

Chloro- or *bromo-substituted carboxylic acids* may be prepared by the direct action of halogen on the acid.

With the exception of formic acid the majority of the fatty acids are little affected by ordinary oxidising agents. Organic acids react with hydrogen peroxide to yield per-acids, such as per-formic acid and per-acetic acid.[1]

When a solution of a carboxylic acid in concentrated sulphuric acid is treated with a chloroform solution of hydrazoic acid, the carboxyl group is converted into an amino group. This reaction is especially useful with the higher homologues and gives good yields.

$$R.COOH+N_3H = R.NH_2+CO_2+N_2.$$

On treatment with concentrated sulphuric acid the tertiary acids, in particular, undergo decomposition to give carbon monoxide and the corresponding carbinols.[2]

Other changes undergone by carboxylic acids have already been mentioned in previous chapters; compare pp. 108, 110, 144, 170, 176.

With regard to the catalytic action of finely divided metals, see Mailhe, *Ch. Zeit.*, **1919**, 242, 254.

An important biological process is the *oxidation of fatty acids at the β-carbon atom* to give lower acids. This was discovered by Knoop, who found that phenyl propionic acid introduced as food was eliminated in the urine as benzoic acid (in the form of hippuric acid): $C_6H_5.CH_2.CH_2.COOH \longrightarrow C_6H_5.COOH$. In diabetic patients butyric acid becomes transformed into β-hydroxy-butyric acid: $CH_3.CH_2.CH_2.COOH \longrightarrow CH_3.CHOH.CH_2.COOH$. By further oxidation the latter probably oxidises to the β-ketonic compound aceto-acetic acid, which readily decomposes into acetone and carbon dioxide (pp. 188 and 261): $CH_3.CO.CH_2.COOH \longrightarrow CH_3.CO.CH_3+CO_2$. On the other hand, benzoic acid, $C_6H_5.COOH$, and phenylacetic acid, $C_6H_5.CH_2.COOH$, in which β-oxidation cannot occur, are unchanged in the organism. Dakin[3] and Neubauer have shown that ammonium salts of fatty acids can be disrupted at the β-position by purely chemical oxidation, using hydrogen peroxide or potassium persulphate.

Methods of Formation.—Of the numerous reactions available for this purpose only the most important are described here.

Saturated monobasic acids are produced:

1. By oxidation of the corresponding primary alcohol or aldehyde (pp. 140 and 175).

2. By allowing alkyl iodides to react with potassium cyanide, and hydrolysing the alkyl cyanide or nitrile so formed.

$$\underset{\text{Methyl cyanide (Aceto-nitrile)}}{CH_3.C:N}+2H_2O = \underset{\text{Acetic acid.}}{CH_3.CO_2H}+NH_3$$

In this reaction we may assume the intermediate formation of the compound

[1] J. d'Ans and W. Frey, *Ber.*, 1912, **45**, 1845. [2] A. Bistrzycki, *Ber.*, 1907, **40**, 4370; 1908, **41**, 1665. [3] *Am. Ch. J.*, 1910, **44**, 41.

$CH_3.C(OH)_3$ with three hydroxyl groups attached to the same carbon atom. Such compounds are not stable (p. 140) and immediately lose a molecule of water to yield carboxylic acids. These hypothetical compounds have been termed ortho-acids and give quite stable esters, *e.g. ortho-formic ester*, $H.C(OC_2H_5)_3$.

3. By Wanklyn's reaction, which is of theoretical importance as affording a simple means of passing from the metallo-organic compounds to the acids. It consists in the action of carbon dioxide on sodium alkyls,

$$CH_3.Na + CO_2 = CH_3.CO.ONa$$

Sodium methyl — Sodium acetate.

The interest of this reaction lies in its simplicity. Unfortunately the alkyl derivatives of alkali metals are unstable and difficult to prepare, so that the method is of little practical value.

4. Carboxylic acids may be readily synthesised by the analogous method of Grignard, by treating alkyl magnesium halides in ethereal solution with carbon dioxide and decomposing the additive compound so formed with dilute sulphuric acid.

$$R.Mg.X + CO_2 = R.CO.O.MgX$$
$$R.CO.OMgX + H_2O = R.CO.OH + HO.MgX$$

5. By the action of carbon monoxide on alcoholates at high temperatures, *e.g.*,

$$CH_3.ONa + CO = CH_3.COONa$$

6. The hydrolysis of acetoacetic ester and its derivatives is a useful method for the preparation of monocarboxylic acids. This is described in detail later.

7. On the technical scale the higher fatty acids are prepared by the hydrolysis of fats.

8. In the animal organism fatty acids are converted into lower acids by oxidation at the β-carbon atom (see previous page).

9. Lower fatty acids are also formed by the reductive degradation of amino-acids.[1]

Isomerism.—The number of structural isomerides theoretically possible for a carboxylic acid of given carbon content is the same as that for the corresponding aldehyde or primary alcohol, since the isomerism depends on the different arrangement of the carbon atoms in the hydrocarbon radical united to the carboxyl group. Among the first three members of the series, therefore, no isomerism is possible. The fourth, however, exists in two isomeric forms.

Formic acid, *methane acid, acidum formicum*, $H.COOH$, occurs in ants, stinging nettles and many liquids of animal origin, such as perspiration and urine; it is obtainable from any of these sources by distillation with water. It may be formed according to the general methods given above, but is usually prepared by one of the following special methods.

Formic acid was originally obtained from oxalic acid by heating

[1] C. Neuberg and Rosenberg, *Biochem. Zeitschr.*, 1907, **7**, 199. Neuberg, *ibid.*, 1911, **37**, 490.

it with glycerol at 100° to 110° (Berthelot). Under these conditions the oxalic acid decomposes with the formation of certain intermediate products to yield chiefly carbon dioxide and formic acid.[1]

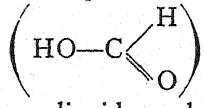
$$\underset{\text{Oxalic acid.}}{HOOC.COOH} = CO_2 + H.COOH$$

Recently it has been manufactured by heating carbon monoxide with soda lime or sodium hydroxide. From the sodium formate thus produced, the pure anhydrous acid is prepared by distillation with sodium hydrogen sulphate.

$$CO + NaOH = H.COONa$$

From dilute solutions the anhydrous acid is isolated by treatment with litharge and decomposing the dried lead salt with hydrogen sulphide at 100°.

Anhydrous formic acid melts at 8·6°, boils at 100·6°, and has a penetrating pungent odour. It is strongly corrosive and raises blisters on the skin. With water, alcohol and ether it is miscible in all proportions. The acid gives rise to salts known as *formates*, all of which dissolve in water, although those of lead and silver are only sparingly soluble.

Owing to the presence of an aldehyde grouping in the molecule, formic acid  tends to undergo oxidation with the formation of carbon dioxide and water, and in this respect differs from all its homologues.

$$HCOOH + O = CO_2 + H_2O$$

Consequently it is a reducing agent, as is shown by its behaviour with silver and mercury salts. When heated with formic acid in aqueous solution the former yield a silver mirror and the latter mercurous salts.

Above 160° formic acid decomposes into carbon dioxide and hydrogen. The same reaction takes place at ordinary temperature under the catalytic influence of finely divided rhodium, iridium, or ruthenium, and less readily with spongy platinum. From this it may be concluded that the molecule has a tendency to split off molecular hydrogen according to the equation $H.COOH = CO_2 + H_2$. The reduction of formic acid by the addition of hydrogen would therefore be expected to present special difficulty and in actual fact, even under the most diverse experimental conditions, it is only possible to obtain minute yields of formaldehyde or methyl alcohol by the reduction of formic acid or its salts with hydrogen. It should be noted, however, that good yields of formaldehyde or methyl alcohol may be obtained by auto-reduction,[2] by heating the acid with a suitable contact agent.

[1] See Chattaway, *J. C. S.*, 1914, 105, 151. [2] K. A. Hofmann and Schibsted, *Ber.*, 1918, 51, 1389, 1398. For the catalytic decomposition of free formic acid see Sabatier and Mailhe, *C.*, 1911, II, 15.

When formic acid is warmed with concentrated sulphuric acid it decomposes smoothly into pure carbon monoxide and water.

$$HCOOH = H_2O + CO$$

Acetic Acid, *Ethane Acid, Acidum aceticum,* $CH_3.COOH$

Salts of acetic acid are found in the saps of many plants and also in perspiration. From the practical standpoint the acid is one of the most important of the organic acids. It is prepared technically by the oxidation of dilute ethyl alcohol (wine, beer, etc.), by the dry distillation of wood and more recently from acetylene as starting material.

I. In the preparation of dilute acetic acid or *vinegar* from liquids containing alcohol, the oxidation is brought about by the action of air under the influence of bacteria, chiefly *Bacterium aceti.* This acetic fermentation occurs during the souring of beer or wines and leads to the formation of white or wine vinegar. Fermented liquids containing a small proportion of alcohol are utilised in this preparation. A more modern method known as the *quick vinegar process* is conducted in the following manner.

Large wooden vats are filled with basket-work or beech shavings moistened with strong vinegar containing acetic bacteria. The basket-work serves on the one hand to present a large surface of liquid to the oxidising action of the air, and on the other provides a suitable medium for the growth of the bacteria. The tubs are fitted with a perforated cover and the alcoholic liquid is run in and allowed to trickle slowly over the shavings. Air enters through holes in the lower walls of the vessel and passes upward in the opposite direction to the flow of the liquid. Oxidation is completed by repeating the process several times, the temperature being maintained at 30° to 35°. The whole reaction lasts about fourteen days and yields a table vinegar with about 6 to 7 per cent. of acetic acid.

II. Stronger acetic acid is prepared by the dry distillation of wood (see p. 145). The liquid products of distillation separate into a lower layer of wood tar and an upper aqueous layer known as pyroligneous acid. The chief constituents of the latter, apart from water, are acetic acid (10 per cent.), methyl alcohol (1 to 2 per cent.) and acetone (0·5 per cent.). After removal of tar, the crude pyroligneous acid is distilled from a copper vessel and the distillate trapped in milk of lime, by which means acetic acid and its homologues are retained as calcium salts. Methyl alcohol and acetone, being volatile, pass on and are condensed in a special apparatus. The raw acetate of lime is freed from tarry matter and dried, when it constitutes the "grey acetate" of commerce (containing 80 per cent. of calcium acetate), from which crude 70 to 75 per cent. acetic acid is generally prepared by direct distillation with sulphuric acid. In another process the crude acetate is converted into sodium acetate by treatment with sodium sulphate. Sodium acetate crystallises exceptionally well and is readily freed from the accompanying salts of

homologous acids (*e.g.* propionic and butyric acids). The dried sodium acetate is treated with concentrated sulphuric acid, and pure acetic acid distilled over. The pure acid solidifies on cooling and comes on to the market under the name of *glacial acetic acid*. The manufacture of glacial acetic acid from sodium acetate is now rarely carried out, as it is almost exclusively prepared by rectification of the 70 to 75 per cent. acid obtained from "grey" acetate of lime. In this case sulphurous acid and dilute acetic acid distil over first, followed by glacial acetic acid and finally propionic and butyric acids.

III. Water combines with acetylene under the influence of mercury salts to form acetaldehyde, which on oxidation may be converted into acetic acid. The development of this reaction has resulted in the manufacture of acetic acid from calcium carbide.

Properties.—Anhydrous acetic acid melts at 16·6° to a corrosive liquid of pungent smell, which boils at 118°. In contact with the skin it produces painful wounds. It is specifically heavier than water, with which it mixes in all proportions, solution being accompanied by liberation of heat and contraction in volume. On adding water to acetic acid the specific gravity first rises, but falls on further dilution. Hence it is not possible to ascertain the strength of an aqueous mixture from specific gravity data alone. The acid is hygroscopic, and stable towards oxidising agents such as chromic acid and potassium permanganate. Since it is an excellent solvent for many organic compounds it is often employed as such in oxidation reactions. Pure acetic acid should not decolorise one drop of a solution of potassium permanganate.

Acetic acid gives rise to salts known as *acetates*, most of which are soluble in water. *Silver acetate* is only sparingly soluble. The following are of technical importance: *sodium acetate*, $NaC_2H_3O_2+3H_2O$, used for artificial cooling; *lead acetate* or *sugar of lead*, $Pb(C_2H_3O_2)_2+3H_2O$; and *basic acetate of lead*, $Pb(OH)(C_2H_3O_2)$, used in the manufacture of lead preparations (e.g. *white lead*).

Acetates of aluminium, chromium, iron and *copper* are largely employed as mordants in dyeing and printing.

Propionic acid, *methyl-acetic acid*, $CH_3.CH_2.COOH$, may be prepared by the oxidation of normal propyl alcohol or by the hydrolysis of ethyl cyanide. It is a liquid of b.p. 141°, which resembles acetic acid. Propionic acid is thrown out of its aqueous solution in the form of an oil by the addition of salts.

Butyric Acids, $C_3H_7.COOH$

Two structural isomerides of this acid are possible:

1. **Normal butyric acid,** *fermentation butyric acid, ethyl-acetic acid*, $CH_3.CH_2.CH_2.COOH$, occurs as the glyceryl ester (*butyrin*) in butter, and in the free state in perspiration. It is formed by the general methods available for the preparation of fatty acids, and is known as fermentation butyric acid owing to its production under certain conditions during

the fermentation of sugar, starch or lactic acid. It is a viscous, unpleasant smelling liquid, b.p. 163°.

2. **Isobutyric acid,** *dimethyl-acetic acid*, $(CH_3)_2CH.COOH$, boils at 154°. It resembles butyric acid in its properties, but is more easily oxidised. The calcium salt differs from that of normal butyric acid in being more soluble in hot water than in cold.

Valeric Acids, $C_4H_9.COOH$

Four structural isomerides are possible, all of which are known, viz. :—

Normal valeric acid, $CH_3.CH_2.CH_2.CH_2.COOH$, b.p. 185°.
Isovaleric acid, $(CH_3)_2CH.CH_2.COOH$, b.p. 175°.
Methyl-ethyl-acetic acid, $(CH_3)(C_2H_5)CH.COOH$, b.p. 177°.
Trimethyl-acetic acid, $(CH_3)_3C.COOH$, b.p. 164°.

Isovaleric acid, *ordinary valeric acid*, $(CH_3)_2CH.CH_2.COOH$, occurs in the free state in many plants, particularly in valerian root, from which it is prepared by boiling with aqueous sodium carbonate. The product so obtained is the ordinary valeric acid, *Acidum valerianicum*, of pharmacy, and contains also some optically active methyl-ethyl-acetic acid. A similar mixture is obtained by the oxidation of fermentation amyl alcohol with chromic acid.

Higher Fatty Acids, Oils, Fats, Waxes[1] and Soaps

Of the higher fatty acids, the normal members of the series with an even number of carbon atoms are found as esters in oils and fats of vegetable and animal origin. The most noteworthy of these are *palmitic acid*, $C_{16}H_{32}O_2$, melting at 62°, and *stearic acid*, $C_{18}H_{36}O_2$, melting at 69°. In frequent association with these two compounds are certain unsaturated acids, such as the liquid *oleic acid*, $C_{18}H_{34}O_2$. Oils and fats consist mainly of mixtures of the neutral glyceryl esters of these three acids, formed, as illustrated in the following equation, by the combination of the trihydric alcohol glycerol with three molecules of monobasic acid.

$$\begin{array}{l} CH_2.OH \\ | \\ CH.OH \\ | \\ CH_2.OH \\ \text{Glycerol} \end{array} + 3C_{15}H_{31}.COOH = \begin{array}{l} CH_2.O.CO.C_{15}H_{31} \\ | \\ CH.O.CO.C_{15}H_{31} \\ | \\ CH_2.O.CO.C_{15}H_{31} \\ \text{Palmitin (Glyceryl tripalmitate)} \end{array} + 3H_2O$$

(Palmitic acid)

Waxes differ chemically from fats in being fatty acid esters, not of glycerol, but of higher monohydric alcohols of the methyl alcohol series, such as cetyl alcohol, $C_{16}H_{33}OH$ (in *spermaceti*) and myricyl alcohol, $C_{30}H_{61}OH$ (in *beeswax*). In addition, they also contain higher alcohols and acids in the uncombined state.

Of the glyceryl esters of the three acids named above, known as

[1] See J. Lewkowitsch, *Chemical Technology and Analysis of Oils, Fats and Waxes.*

palmitin, stearin and olein respectively, the last has a considerably lower melting-point than the others.

Palmitin . . .	$C_3H_5(O.CO.C_{15}H_{31})_3$	m.p. 63°
Stearin . . .	$C_3H_5(O.CO.C_{17}H_{35})_3$	,, 65·5°
Olein	$C_3H_5(O.CO.C_{17}H_{33})_3$	,, −6°

It follows, therefore, that the melting-point of a fat or oil, and its consistency at the ordinary temperature, depend very largely on the relative proportions of the glycerides present.

These oils and fats are obtained only from animal and vegetable sources. In plants they function like starch as food reserves, and for this purpose they are accumulated in the seeds and tubers. Animals also use vegetable oils and fats as food, employing them to build up new fats, which are deposited in the body and if required are available as reserves in time of hunger.

Oils and fats are prepared from naturally occurring products by expressing, melting or boiling out, or by extraction with solvents. Those intended for table use are generally expressed or melted out. When intended for other purposes all four processes may come into operation. Frequently the melting-out process is performed under pressure.

Fats are insoluble in water, and only sparingly soluble in alcohol; they dissolve readily in ether, carbon disulphide, benzine, chloroform and similar solvents.

On heating with alkalis (lime, magnesia, etc.), mineral acids, or with water at high temperature and pressure, fats are hydrolysed to form glycerol and fatty acids :—

$$\begin{array}{l} CH_2.O.CO.C_{15}H_{31} \\ | \\ CH.O.CO.C_{15}H_{31} \\ | \\ CH_2.O.CO.C_{15}H_{31} \\ \text{Palmitin} \end{array} + 3H_2O = 3\underset{\text{Palmitic acid}}{C_{15}H_{31}.COOH} + \begin{array}{l} CH_2.OH \\ | \\ CH.OH \\ | \\ CH_2.OH \\ \text{Glycerol.} \end{array}$$

This hydrolysis is brought about by the use of alkalis in the manufacture of soaps, which are alkali salts of the fatty acids. Hence the above reaction is sometimes termed *saponification*.

Hydrolysis may also be effected at relatively low temperatures (below 40°) by the action of the fat-hydrolysing enzyme *lipase* on an aqueous emulsion of the fat. Ferments of this type are present in the digestive organs and also in plants.[1]

The **free fatty acids** required for the production of candles and glycerol, which is utilised nowadays for a great many purposes, are usually prepared by hydrolysing fats with sulphuric acid, or with water alone

[1] An industrial process for converting fats into fatty acids and glycerol depends on the action of an enzyme occurring in the castor bean. After removing the oil present in the beans the residue is ground up with the fat and mixed with a dilute (*e.g.* $\frac{1}{10}$ normal) solution of sulphuric acid, when an emulsion is formed. At a temperature of 30° to 40° the fatty acids separate out in the pure state during the space of two or three days, while glycerol collects in the solution to the extent of 30 to 40 per cent. See Hoyer, *Ber.*, 1902, **35**, 3988; 1904, **37**, 1436; *C.*, 1905, **II**, 582; 1907, **I**, 646.

under high pressure (15 to 16 atmospheres) and temperature (*ca.* 200°). The raw materials most frequently employed are tallow, lard, coco-nut oil and palm oil.

As obtained by this process the mixture of fatty acids forms a semi-solid mass at ordinary temperatures, since it contains liquid oleic acid in addition to solid palmitic and stearic acids. Oleic acid is removed under pressure and used for the manufacture of soap. After admixture with a little wax to prevent crystallisation the solid acids are used in the production of " stearine " candles.

It has been stated that **soaps** are salts of fatty acids, and chiefly the alkali salts of palmitic, stearic and oleic acids. They are prepared by saponifying fats by boiling with caustic soda or potash. The reaction with palmitin, a fat very widely distributed in nature, is expressed by the equation :—

$$\begin{array}{l} CH_2.O.CO.C_{15}H_{31} \\ | \\ CH.O.CO.C_{15}H_{31} \\ | \\ CH_2.O.CO.C_{15}H_{31} \\ \text{Palmitin} \end{array} + 3NaOH = \underset{\substack{\text{Sodium palmitate} \\ \text{(a soap)}}}{3C_{15}H_{31}.COONa} + \begin{array}{l} CH_2.OH \\ | \\ CH.OH \\ | \\ CH_2.OH \\ \text{Glycerol.} \end{array}$$

Hard soaps are sodium salts containing a preponderance of solid acids ; *soft soaps*, on the other hand, are potassium salts with a high proportion of oleate. These soaps differ in solubility, and when potassium soaps are treated with excess of brine they are converted into the less soluble sodium soaps (" salting out " process).

$$\underset{\substack{\text{Potassium palmitate} \\ \text{(soft soap)}}}{C_{15}H_{31}.COOK} + NaCl = \underset{\substack{\text{Sodium palmitate} \\ \text{(hard soap).}}}{C_{15}H_{31}.COONa} + KCl$$

The following procedure is adopted in the manufacture of curd soap from tallow.

The fat is first placed in a large cylindrical vessel and a dilute solution of caustic soda (" lye " of about 15° Bé.) introduced, amounting to about one-quarter of the theoretical quantity. Steam is blown in and the mixture vigorously boiled. An emulsion is first formed, and as the alkali enters into reaction, additional amounts are run in slowly till finally an excess is present and the mass appears clear. The soap is thrown out of solution by the addition of salt and allowed to settle, after which the lower layer of liquid (sweet lye), containing the glycerol, is run off from below. The soap is then again boiled with water and alkali to complete the saponification.

The lye is once more run off and the soap boiled up with the requisite amount of water (hydration) and again allowed to settle. A dark coloured lye containing metallic soaps, chiefly of iron, separates out at this stage. The solid soap is finally removed, cut up and dried.

Sodium and potassium soaps dissolve in a small amount of water to give a clear solution, but in the presence of much water hydrolytic dissociation of the salt takes place with the formation of free acid and alkali. According to conditions, the free acid may remain suspended in the liquid in the form of oily drops or be precipitated in combination with the soap as a sparingly soluble acid salt. On the liberation of free alkali depends the cleansing action of soap. At this dilution the alkali

loosens grease and dirt without attacking the skin or the material which is being cleaned. At the same time the precipitated salts envelop the particles of detached fat and dirt and prevent them from being again deposited on the fibres.

Synthetic detergents are now used for washing purposes. They are prepared by the hydrogenation of fatty acids (*e.g.* palmitic, stearic, oleic and lauric acids) at high temperature and pressure using a copper salt catalyst; the resulting alcohols, R.OH, are then converted into the sodium alkyl sulphates, $R.O.SO_2.ONa$. These salts lather well and are unaffected by hard water. Unlike ordinary soaps they are not hydrolysed in solution to give free alkali, hence they do not cause woollens to shrink.

The term " soap " includes insoluble and sparingly soluble salts of fatty acids, such as those of calcium, lead (lead plaster), zinc, aluminium, tin and others, many of which are used industrially.

Calcium soaps are so sparingly soluble that they are deposited on mixing sodium or potassium soaps with solutions of calcium salts.

$$\underset{\text{Potassium palmitate}}{2C_{15}H_{31}.COOK} + CaCl_2 = \underset{\text{Calcium palmitate.}}{(C_{15}H_{31}COO)_2Ca} + 2KCl$$

For this reason water containing lime salts gives no lather with soap, the lime soap separating out as a white flocculent precipitate. Such water is called " hard " and is difficult to use for washing purposes.

Lead plaster contains lead soaps and is usually obtained by heating soft fats (lard or oil) or oleic acid with litharge till the product is easily moulded by the warmth of the hand but solidifies on cooling. The plaster still contains all the liberated glycerol and some unchanged fat. *Soaps of lead* and *manganese* are also utilised in the preparation of varnishes. *Aluminium soaps* are used in waterproofing.

Among the still higher acids of this series are *arachic acid*, $C_{19}H_{39}COOH$ (present as the glyceride in earth-nut oil); *behenic acid*, $C_{21}H_{43}COOH$; *lignoceric acid*, $C_{23}H_{47}COOH$ (in earth-nut oil and wood tar); *cerotic acid*, $C_{25}H_{51}COOH$ (as ester in beeswax); *melissic acid*, $C_{29}H_{59}COOH$ (in carnauba wax and beeswax).

Phosphatides.—Closely related to the fats is a class of complex substances known as phosphatides (lipoids) which is of great physiological importance. These compounds are glycerides in which the organic acid residues (in either the α- or β-positions in the glycerol molecule) are partially replaced by groups containing phosphoric acid and a base such as choline (p. 246) or hydroxy-ethylamine (p. 245). Phosphatides occur widely distributed in the animal and vegetable kingdoms, *e.g.* in yolk of egg, brain and seeds. Their constitution is deduced from their behaviour on hydrolysis with dilute acids or alkalis.

One of the best known representatives is **lecithin** (apparently a mixture of closely related products) which decomposes into choline and *distearyl-glycerol-phosphoric acid* (I). On further hydrolysis the latter yields two molecules of stearic acid, one molecule of phosphoric acid and glycerol. Lecithin (II) is therefore considered to be the choline ester of I. Various *α-lecithins* are known differing from the above in

the partial or complete replacement of the stearic groups by palmitic, oleic or similar acid residues. *β-Lecithins* contain the phosphoric complex

I. CH_2—O.$COC_{17}H_{35}$
(β) CH—O.$COC_{17}H_{35}$
(α) CH_2—OPO$(OH)_2$

II. CH_2—O.$COC_{17}H_{35}$
CH—O.$COC_{17}H_{35}$
CH_2—OPO(OH)O.CH_2.CH_2.N$(CH_3)_3$OH

in the β-position. Lecithins are very hygroscopic, unstable in air, and dissolve readily in alcohol and ether.

Kephalin, which commonly accompanies lecithin in the crude state, is a phosphatide derived from hydroxy-ethylamine instead of choline. It is separated from lecithin by means of its low solubility in alcohol.

II.—UNSATURATED MONOBASIC ACIDS

1. Oleic Acid Series, $C_nH_{2n-1}COOH$

The best known member of the class is oleic acid, from which the series takes its name. These acids may be regarded as derivatives of the olefins C_nH_{2n}, and stand in the same relationship to the fatty acids as the olefins to the paraffins.

They may be obtained by methods analogous to those given for the fatty acids; also by the general methods available for the preparation of unsaturated compounds, *e.g.* by the removal of hydrogen halide from monohalogen substitution products of fatty acids (I), or of water from the corresponding monohydroxy acids (II).

I. $CH_2Cl.CH_2.COOH \longrightarrow CH_2:CH.COOH$
Chloro-propionic acid — Acrylic acid.

II. $CH_3.CHOH.CH_2.COOH \longrightarrow CH_3.CH:CH.COOH$
Hydroxy-butyric acid — Crotonic acid.

In chemical and physical properties these compounds strongly resemble the fatty acids, but they differ from them in certain points, particularly in their *addition reactions*. They combine with chlorine, bromine and iodine to form dihalogen derivatives, and with hydrogen halides to give monohalogen derivatives of the fatty acids. In the latter case halogen usually attaches itself to the carbon atom further away from the carboxyl group.

$CH_2:CH.COOH + 2Cl = CH_2Cl.CHCl.COOH$
Acrylic acid — Dichloropropionic acid.

Unsaturated acids may be converted into saturated compounds by catalytic reduction. Thus when oleic acid is treated with hydrogen at ordinary temperatures in the presence of colloidal palladium it yields stearic acid. Mixtures of glycerides of saturated and unsaturated aliphatic acids, such as are present in animal and vegetable fats, may also be treated in the same manner. Castor oil, olive oil and cod-liver oil, which are rich in unsaturated glycerides, can be practically completely reduced by this process and thereby transformed into a crystalline, tallow-like mass of high melting-point. It is a matter of technical importance that

other and cheaper catalysts, such as finely divided nickel (*Sabatier-Senderens process*), may be used in place of palladium for this purpose, and also that pure hydrogen may be replaced by the gaseous mixtures of hydrogen obtained as industrial by-products. Under such treatment oils and soft fats generally yield a harder product which has many advantages, including a more pleasant taste and improved keeping qualities as compared with the starting material. For this reason the *technical hardening of fats* is of great practical importance [1] in the manufacture of margarine.

Unsaturated acids unite with ozone to form unstable ozonides. The ozonide of isocrotonic acid is a yellow, extremely explosive syrup, which decomposes energetically with water. It evolves oxygen on standing and regenerates the original acid.

Another characteristic of unsaturated acids is the ease with which they undergo *oxidation* (*cf.* p. 122). With mild oxidising agents the first step is the addition of two hydroxyl groups to yield a dihydroxy acid (III). On further oxidation, disruption occurs at the point originally occupied by the double bond and two molecules of saturated acids are formed (IV). In this manner it is possible to ascertain the position of the double bond in an unsaturated acid.

III. $CH_3.CH{=}CH.COOH + H_2O + O \longrightarrow CH_3.CHOH.CHOH.COOH$
(Crotonic acid.)

IV. $CH_3.CHOH.CHOH.COOH + 3O \longrightarrow CH_3.COOH + COOH.COOH + H_2O$
(Acetic acid; Oxalic acid.)

The molecule may also be disrupted by *fusion with sodium or potassium hydroxide* in the presence of air, saturated fatty acids being again produced:

$CH_3.CH{=}CH.COOH + O + H_2O \longrightarrow CH_3.CO_2H + CH_3.CO_2H$
(Crotonic acid; Acetic acid; Acetic acid.)

In this case, however, the chain does not always break at the point originally occupied by the double bond, since under the influence of alkalis the latter is frequently displaced towards the carboxyl group.[2] Fusion with alkali cannot therefore be employed to determine the position of the double bond.

Isomerism among the acids of the oleic series may be of two kinds: (1) *structural isomerism* caused by a different arrangement of the carbon atoms in the hydrocarbon chain, or a different position of the double bond, and (2) *geometrical isomerism* (see p. 48).

Acrylic acid, $CH_2 : CH.COOH$, is formed by oxidising acrolein with silver oxide, and is best prepared from glycol-chlorohydrin as follows:

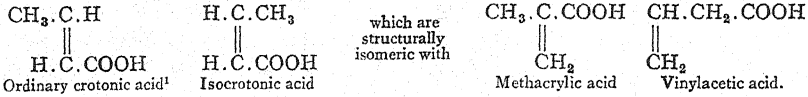
$$HO.CH_2.CH_2Cl \longrightarrow HO.CH_2.CH_2CN \longrightarrow CH_2 : CH.COOH$$ [3]

It melts at 7°, boils at 141°, and has a smell resembling that of acetic acid.

[1] See Crossley, *The Pharmaceutical Journal and Pharmacist*, 1914, **92**, 637, 676. C. Ellis, *J.S.C.I.*, 1912, **31**, 1155; T. Shaw, *ibid.*, 1914, **33**, 771. [2] Fittig, *Ann.*, 1894, **283**, 47, 269.
[3] J. H. N. van der Burg, *Rec. trav. chim.*, 1922, **41**, 21.

It slowly polymerises on standing, and when reduced yields propionic acid. With hydriodic acid it forms β-iodopropionic acid.

Crotonic acid, $C_4H_6O_2$, is known in two stereoisomeric forms, namely,



Ordinary or solid crotonic acid (m.p. 72°, b.p. 180°) may be obtained by the general methods given above, or by oxidation of crotonic aldehyde. It is most readily prepared by heating malonic acid, $CH_2(COOH)_2$, with paraldehyde and acetic anhydride. On reduction with zinc and sulphuric acid it is converted into normal butyric acid, showing that it contains no branched chain. With nitric acid it breaks up, forming acetic acid and oxalic acid, whereas permanganate oxidises it to dihydroxy-butyric acid. When dissolved in toluene and irradiated with ultra-violet light it isomerises into isocrotonic acid.

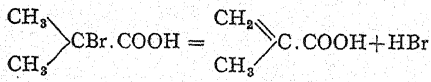
Iso- or allocrotonic acid (m.p. 15°, b.p. 169°) may be prepared by reducing chloro-isocrotonic acid with sodium amalgam and is very similar to the ordinary acid in properties. On vigorous reduction it also yields normal butyric acid. It is readily transformed into the isomeric acid, the change taking place to some extent merely on distillation. A more complete transformation may be effected by heating at 170° to 180° in a sealed tube, or by the combined action of sunlight and traces of bromine on a solution of the acid in water or carbon disulphide. Many similar examples of stereoisomeric change are met with in organic chemistry.

Ozone reacts with an aqueous solution of isocrotonic acid, breaking up the molecule and forming acetaldehyde and glyoxalic acid. From this reaction the constitution of the acid may be deduced.

$$CH_3.CH:CH.COOH+O_3+H_2O = CH_3.CHO+O{:}CH.COOH+H_2O_2$$

Glyoxalic acid.

Methacrylic acid, *2-methyl-2-propene-1-acid* (m.p. 15°, b.p. 160·5°), occurs in oil of Roman camomile, *Anthemis nobilis*, and is formed from bromo-isobutyric acid by elimination of HBr:



On reduction methacrylic acid yields isobutyric acid. It combines with bromine to give αβ-dibromo-isobutyric acid, thus confirming the above constitutional formula. Methyl methacrylate is used in preparing synthetic plastics of great transparency (*perspex*, see p. 857).

Vinyl-acetic acid (b.p. 71° at 13 mm.) has been obtained synthetically. When boiled with caustic soda it is converted into ordinary crotonic acid and β-hydroxybutyric acid.

Oleic acid, $CH_3.(CH_2)_7.CH:CH.(CH_2)_7.COOH$, is found as the glyceryl ester, *triolein*, especially in the fatty oils (such as almond oil or olive oil), from which it is obtained as a by-product after hydrolysis in the manufacture of stearic acid (see p. 200). By taking advantage of the solubility of the lead salt in ether it may be separated from stearic and palmitic acids. At ordinary temperatures it is a colourless, almost odourless and tasteless liquid. At 4° it solidifies to a mass of colourless needles, which melt again when the temperature is raised to 14°. In contact with air, however, it rapidly becomes yellow owing to oxidation, and acquires a sour, rancid smell. Oleic acid gives stearic acid on reduction and

[1] K. v. Auwers and H. Wissebach, *Ber.*, 1923, 56, 715.

dibromostearic acid on treatment with bromine, hence like stearic acid it contains a normal straight chain of carbon atoms. Further, the double bond must be situated in the middle of the molecule, since careful oxidation leads to the formation of a mixture of *pelargonic acid*, $C_8H_{17}.COOH$, and *azelaic acid*, $HOOC(CH_2)_7COOH$.

Nitrous acid converts oleic acid into a solid compound, **elaïdic acid**, m.p. 51°. This possesses the same structure as oleic acid, with which it is stereoisomeric. The relationship between oleic and elaïdic acids is thus similar to that existing between the two crotonic acids. Oleic acid is the *cis*- and elaïdic acid the *trans*- form.[1]

Proof of the stereoisomerism of oleic and elaïdic acids is based on the observation that the dibromides of both these acids can be converted into the same *stearolic acid*, $C_8H_{17}C{\equiv}C(CH_2)_7COOH$. Additional confirmation is found in the manner in which the ozonides of the two acids are decomposed by water.[2]

$$CH_3.(CH_2)_7.\underset{\displaystyle O\text{——}O}{CH.O.CH}.(CH_2)_7.CO_2H+H_2O =$$

Ozonide of oleic or elaïdic acid

$$\underset{\text{Nonyl-aldehyde}}{CH_3.(CH_2)_7.CH{:}O}+\underset{\text{Half aldehyde of azelaic acid.}}{O{:}CH.(CH_2)_7.COOH}+H_2O_2$$

In the presence of air the half aldehyde of azelaic acid is rapidly oxidised to azelaic acid.

Oleic acid is used in the manufacture of soap.

Petroselic acid, $CH_3.(CH_2)_{10}.CH:CH.(CH_2)_4.COOH$, m.p. 33° to 34°, is obtained by the hydrolysis of a fat isolated from oil of parsley seeds. With small amounts of nitrous acid it yields a stereoisomeric acid melting at 54°.

Glutaconic acid, $HOOC.CH_2.CH:CH.COOH$, exhibits an interesting type of isomerism (see p. 66).

Among acids containing two double bonds in the molecule the most important are linoleic and sorbic acids.

Linoleic acid, $CH_3.(CH_2)_4.CH:CH.CH_2.CH:CH.(CH_2)_7.COOH$, b.p. 229° under 16 mm. pressure, occurs as the glyceride in linseed oil, hemp oil, poppy-seed oil, and other drying oils. On reduction with hydriodic acid and phosphorus it yields stearic acid. In air it rapidly absorbs oxygen to form a hard resinous product.

Sorbic acid, $CH_3.CH:CH.CH:CH.COOH$, m.p. 134·6°, is found in the unripe berries of the mountain ash. It may be prepared synthetically by warming croton-aldehyde with malonic acid in the presence of pyridine as condensing agent.

$$\underset{\text{Crotonic aldehyde}}{CH_3.CH:CH.CHO}+\underset{\text{Malonic acid}}{H_2C(COOH)_2} = \underset{\text{Sorbic acid.}}{CH_3.CH:CH.CH:CH.COOH}+CO_2+H_2O$$

Geranic acid, $(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.COOH$, may be obtained by the oxidation of citral (p. 188).

2. Acids containing an Acetylene Bond. Propiolic Acid Series, $C_nH_{2n-3}.COOH$

These acids may be considered to be derivatives of the acetylene hydrocarbons, and are formed from acids of the oleic series in the same manner

[1] J. Böeseken and A. H. Belinfante, *Rec. trav. chim.*, 1926, **45**, 914. C. Paal and H. Schiedewitz, *Ber.*, 1927, **60**, 1221. [2] Harries and Thieme, *Ann.*, 1905, **343**, 311.

as the acetylenes are formed from the olefins, *i.e.* by the addition of halogen and subsequent removal of 2 mols. of hydrogen halide.

$$\underset{\text{Crotonic acid}}{CH_3.CH:CH.COOH} \longrightarrow \underset{\text{Dibromobutyric acid}}{CH_3.CHBr.CHBr.COOH} \longrightarrow \underset{\text{Tetrolic acid.}}{CH_3.C:C.COOH}$$

They are also produced by the action of carbon dioxide on sodium derivatives of the acetylene hydrocarbons.

$$CH:CNa+CO_2 = CH:C.COONa$$

Like the acetylene hydrocarbons, these acids possess additive properties, and yield explosive compounds with ammoniacal solutions of silver and copper.

Propiolic acid, *propargylic acid,* $CH{\equiv}C.COOH$ (m.p. 9°, b.p. 144°), corresponds to propargyl alcohol. It has a smell resembling that of acetic acid and polymerises in sunlight to form a benzene derivative, *trimesic acid,* $C_6H_3(COOH)_3$. On reduction, propiolic acid is converted into propionic acid.

Among other acids may be mentioned *tetrolic acid,* $CH_3.C{\equiv}C.COOH$, m.p. 203°, and *octinic acid,* $CH_3(CH_2)_4C{\equiv}C.COOH$. The methyl ester of the latter is employed as an artificial violet perfume.

XI

Derivatives of Monocarboxylic Acids

I.—DERIVATIVES FORMED BY SUBSTITUTION IN THE CARBOXYL GROUP

1. Esters

Methods of Formation.—In properties and methods of formation the esters of monocarboxylic acids resemble the esters of the mineral acids (see p. 156). Thus they may be prepared by the direct interaction of acid and alcohol, a reversible reaction which proceeds towards equilibrium (p. 157).

$$CH_3.COOH+C_2H_5OH \rightleftharpoons CH_3.COOC_2H_5+H_2O$$

In the preparation of the ester by this method the backward hydrolytic action of the water is reduced to a minimum by the addition of concentrated sulphuric acid or dry gaseous hydrochloric acid.[1] A common method of *esterification* is to boil the organic acid for several hours with excess of the alcohol, to which has been added 3 to 5 per cent. of hydrogen chloride or sulphuric acid (Fischer-Speier method). The ester is then isolated by pouring the mixture into water, in which the alcohol and acid usually dissolve without difficulty, leaving the ester as an insoluble oil.

Sabatier and Mailhe have prepared esters catalytically by the direct action of acids on alcohols in the presence of metallic oxides.[2] At 280° to 300° the esterification proceeds quickly and smoothly, provided the catalyst brings about no marked decomposition of the acid. When, for example, equimolecular amounts of a primary alcohol and an aliphatic

[1] E. Fischer, *Ber.*, 1895, **28**, 3252. Inorganic dehydrating salts may also be used for esterification. [2] Sabatier and Mailhe, *C.*, 1911, **I**, 1196.

acid are passed, in the form of vapour, over titanium oxide at 280° to 290°, a considerable amount of ester is produced.

Other methods of preparing esters have already been mentioned on pp. 131 and 157, and only the corresponding equations for the formation of ethyl acetate need be given here.

$$\underset{\text{Silver acetate}}{CH_3.COOAg}+C_2H_5.I = \underset{\text{Ethyl acetate}}{CH_3.COOC_2H_5}+AgI$$

$$\underset{\text{Acetyl chloride}}{CH_3.CO.Cl}+C_2H_5OH = CH_3.COOC_2H_5+HCl$$

$$\underset{\text{Acetic anhydride.}}{\begin{matrix}CH_3.CO\\ \\ CH_3.CO\end{matrix}\!\!>\!O}+C_2H_5OH = CH_3.COOC_2H_5+CH_3COOH$$

Methyl esters of carboxylic acids are also obtained by the action of dimethyl sulphate on the alkali salts of these acids. The reaction takes place according to the following equation, a salt of methyl sulphuric acid

$$R.COOK+(CH_3)_2SO_4 = R.COOCH_3+CH_3KSO_4$$

also being formed. Better yields appear to be given by the use of salts in the solid state than in solution; it is also preferable to use potassium rather than sodium compounds.

Properties.—The esters of lower molecular weight are colourless liquids with a pleasant fruity odour. Many of them are therefore prepared on a large scale in industry for use as artificial fruit essences. They are generally insoluble in water, but soluble in alcohol and ether. The boiling-point of an ester with a simple alkyl group (CH_3, C_2H_5, C_3H_7) is lower than that of the corresponding acid, but with the entrance of larger alkyl groups the position is reversed.

When esters are superheated with water, or boiled with alkalis or mineral acids, they undergo **hydrolysis** to regenerate the component acids and alcohols (see *saponification* and *hydrolysis*, p. 156).

$$CH_3.COOC_2H_5+H_2O = CH_3.COOH+C_2H_5OH$$
$$CH_3.COOC_2H_5+KOH = CH_3.COOK+C_2H_5OH$$

Owing to the ease with which the alkoxy group, —OR, can be replaced by other groups, esters are very reactive compounds. Thus on treatment with ammonia they are converted into acid amides, and with phosphorus pentachloride into acid chlorides (see below).

When an ethyl ester is warmed with methyl alcohol and a catalyst (*e.g.* CH_3ONa or HCl) a reversible change occurs and the corresponding methyl ester is formed. Other esters and alcohols behave in the same manner. This is known as **alcoholysis.**

For reactions of esters with organo-magnesium halides see p. 144.

Ethyl formate, $H.CO.OC_2H_5$, b.p. 55°, is used for flavouring artificial rum or arrak.

Ethyl orthoformate, $CH(OC_2H_5)_3$, b.p. 146°, is obtained when chloroform is heated with sodium ethoxide in alcoholic solution,

$$CHCl_3+3Na.OC_2H_5 = CH(OC_2H_5)_3+3NaCl$$

and is frequently used for synthetic purposes.

Ethyl acetate, acetic ester, $CH_3.CO.OC_2H_5$, b.p. 78°, is manufactured in large quantities from alcohol, sulphuric acid, and acetic acid or sodium acetate. It is used in the preparation of fruit essences and as a solvent in the manufacture of smokeless powder. On account of its refreshing perfume it is also employed in medicine.

Isoamyl acetate, amyl acetate, $CH_3.CO.OC_5H_{11}$, b.p. 138°, is used as artificial pear essence, and also as fuel in the Hefner standard lamp.

Ethyl butyrate is used as pineapple essence.

Ethyl isovalerate and *isoamyl isovalerate* are employed as apple flavourings.

It has already been explained on p. 198 *et seq.*, that fats and waxes are for the most part esters of higher fatty acids.

2. Acid Chlorides

Acid chlorides are compounds formed by replacing the hydroxyl of an acid with chlorine, and therefore contain the group —CO.Cl.

This change can be brought about by the same reactions as are used for the replacement of the hydroxyl group in alcohols, see p. 129. Acid chlorides may be prepared by the action of phosphorus trichloride or pentachloride on the acid or its alkali salts. In many cases it is more satisfactory to use thionyl chloride, when the only by-products are sulphur dioxide and hydrogen chloride, both of which are gases.

$$\underset{\text{Acetic acid}}{CH_3.COOH}+PCl_5 = \underset{\text{Acetyl chloride.}}{CH_3.CO.Cl}+POCl_3+HCl$$

$$R.COOH+SOCl_2 = R.COCl+SO_2+HCl.$$

An excess of hydrogen bromide or iodide reacts with an acid chloride to give an acid bromide or iodide, *e.g.*

$$R.C\begin{matrix}O\\Cl\end{matrix}+HI \rightleftharpoons R.C\begin{matrix}I\\OH\\Cl\end{matrix} \rightleftharpoons R.C\begin{matrix}I\\O\end{matrix}+HCl$$

Properties.—The lower acid chlorides are colourless liquids with a sharp, irritating smell. Those of higher molecular weight are colourless crystalline compounds. They boil at a lower temperature than the corresponding acids, and generally without decomposition. In air they fume strongly, interacting with moisture to form the corresponding carboxylic acid and hydrochloric acid.

$$CH_3.CO.Cl+H_2O = CH_3.CO.OH+HCl$$

With alcohols and phenols they interact with the production of esters.

$$CH_3.CO.Cl+H.OC_2H_5 = CH_3.CO.OC_2H_5+HCl$$

For this reason acid chlorides, especially *acetyl chloride* and the aromatic compound *benzoyl chloride*, are frequently used for *detecting the presence of hydroxyl groups* in an organic molecule.

They also very readily interact with ammonia and primary and secondary amines (see p. 172).

For their behaviour towards zinc alkyls and magnesium alkyl halides see pp. 144 and 177.

Acetyl chloride, $CH_3.CO.Cl$, b.p. 55°, is prepared by the action of phosphorus trichloride on acetic acid. It is a colourless mobile liquid of pungent smell.

Acetyl nitrate, $CH_3.CO.O.NO_2$, may be obtained by the action of nitric anhydride on acetic anhydride. It has been found to be a very energetic agent for the nitration of aromatic compounds.[1]

3. Acid Anhydrides

These are prepared by the action of acid chlorides on the alkali salts of the acids.

$$CH_3.CO.Cl + CH_3.CO.ONa = \begin{matrix} CH_3.CO \\ CH_3.CO \end{matrix}\!\!>O + NaCl$$

Acetic anhydride.

Acid anhydrides are liquid or solid compounds of neutral reaction, which boil at a higher temperature than the corresponding acids. They possess an unpleasant, pungent smell, and dissolve unchanged in indifferent organic solvents.

In their chemical behaviour towards water, alcohols, phenols and bases, the acid anhydrides resemble acid chlorides, except that they react far less energetically.

Acetic anhydride, $(CH_3.CO)_2O$, is a colourless liquid, b.p. 137°. It is heavier than water and has a smell similar to that of acetic acid. Like acetyl chloride it is a valuable reagent for introducing acetyl groups into alcohols, phenols, and primary and secondary amines.

4. Thio-acids, R.CO.SH

Thio-acids correspond to the thio-alcohols or mercaptans (see p. 161), and are obtained by the action of phosphorus pentasulphide on acids, or by double decomposition between acid chlorides and potassium hydrosulphide. They are liquids of nauseous odour.

$$5CH_3.COOH + P_2S_5 = 5CH_3.CO.SH + P_2O_5$$
$$CH_3.CO.Cl + KSH = CH_3.CO.SH + KCl$$

Thio-acetic acid.

Thio-acetic acid, ethane-thiolic acid, $CH_3.CO.SH$, is a colourless liquid boiling below 100°. It smells of acetic acid and hydrogen sulphide, and may be used for the acetylation of amines.[2]

5. Carbithionic Acids, R.CS.SH

These compounds are produced by the action of carbon disulphide on organo-magnesium halides.

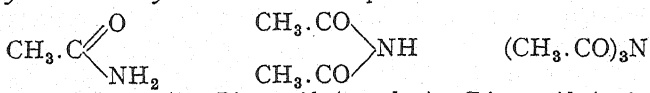
$$R.Mg.Br + CS_2 \longrightarrow R.CS.S.MgBr \longrightarrow R.CS.SH$$

They contain the characteristic grouping —C(:S).SH, which is more strongly acidic than the carboxyl group. The acids are exceedingly unstable and are easily oxidised in air.

[1] A. Pictet and Khotinsky, *Ber.*, 1907, **40**, 1163. [2] Pawlewski, *Ber.*, 1902, **35**, 110.

6. Acid Amides

It has already been seen (p. 167) that the hydrogen of ammonia can be replaced by alkyl groups to form amines. In a similar manner the hydrogen may also be exchanged for acid radicals, when *primary*, *secondary* and *tertiary acid amides* are produced.



Acetamide (primary) Diacetamide (secondary) Triacetamide (tertiary).

If hydrogen is substituted partly by an alkyl group and partly by an acid radical, the product is termed an alkylated acid amide, *e.g.*

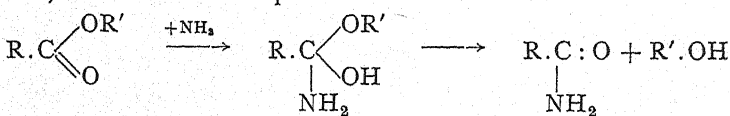
$CH_3.CO.NH.C_2H_5$ Acet-ethylamide $CH_3.CO.N(CH_3)_2$ Acet-dimethylamide.

By far the most important of these compounds are the primary acid amides, commonly known as *acid amides*.

Derivatives of the above types are readily formed by the action of ammonia or amines on acid chlorides, anhydrides or esters :

$$CH_3.CO.Cl+HNH_2 = CH_3.CO.NH_2+HCl$$
$$(CH_3.CO)_2O+2HNH_2 = 2CH_3.CO.NH_2+H_2O$$
$$CH_3.CO.OC_2H_5+HNH_2 = CH_3.CO.NH_2+C_2H_5.OH$$

They are generally prepared from the acid chloride and ammonia, but where this reaction does not proceed in the desired direction, an ester is used in place of the acid chloride. In the latter case the action probably takes place in two stages, an addition compound being first produced, which then decomposes with elimination of alcohol :



Ester Hypothetical intermediate product Acid amide Alcohol.

In practice the reaction is best carried out by shaking the ester with concentrated aqueous ammonia in a closed vessel. Methyl esters are more completely and rapidly converted into amides than their higher homologues.[1]

The amide of an acid can often be prepared by distilling the dry ammonium salt, or more satisfactorily by heating it under pressure for about five hours at 220° to 230°.[2]

$$CH_3.COONH_4 = CH_3.CO.NH_2+H_2O$$

Finally, acid amides can also be obtained from nitriles (cyanides), which take up the elements of water when treated with moderately strong sulphuric acid.

$$CH_3.CN+H_2O = CH_3.CO.NH_2$$

Methyl cyanide Acetamide.

Properties.—With the exception of the fluid formamides, amides are

[1] Hans Meyer, *Monats.*, 1906, **27**, 31. [2] H. Decker, *Ann.*, 1913, **395**, 282.

colourless crystalline compounds, those of lower molecular weight being easily soluble in water. Their boiling-points lie considerably higher than those of the corresponding acids.

In connection with their chemical behaviour it should be noted that acid amides differ from amines in possessing very little basic character. While, therefore, the basic properties of ammonia are retained after the entrance of an alkyl group, they are very strongly diminished by the introduction of an acid radical. Salts such as $CH_3CO.NH_2$, HCl, formed by the combination of an amide with an acid, are known, but they are very unstable and decompose into their original components on treatment with water. On the other hand, amides are also weakly acidic in character, one of the two hydrogen atoms of the amido group being replaceable by metals. Mercury salts of this type are readily formed by boiling an aqueous solution of an amide with mercuric oxide.

$$2CH_3.CO.NH_2+HgO = (CH_3.CO.NH)_2Hg+H_2O$$

A further difference between acid amides and amines is that in the former the bond between carbon and nitrogen is easily disrupted. On boiling with water, or more rapidly on heating with alkalis, the amides are hydrolysed to the acid and ammonia.

$$CH_3.CO.NH_2+H_2O = CH_3.COOH+NH_3$$

Nitrous acid converts primary acid amides into the corresponding acids, with evolution of nitrogen. This reaction is in all respects analogous to the formation of alcohols from primary amines (p. 170).

$$CH_3.CO.NH_2+O:N.OH = CH_3.CO.OH+N_2+H_2O$$

Under the influence of dehydrating agents such as P_2O_5, amides are transformed into nitriles,

$$CH_3.CO.NH_2-H_2O = \underset{\text{Acetonitrile.}}{CH_3.CN}$$

The conversion of acid amides into amines has already been described on p. 169.

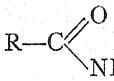
With regard to the *constitution of the amides*, two formulæ are theoretically possible, of which formula I is generally accepted in preference to the iminohydrin structure of formula II.

I. $R-C(=O)-NH_2$ II. $R-C(-OH)=NH$

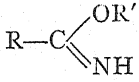
Although certain metallic derivatives of the amides, such as the silver salts, appear to be related to formula II, no reactions are known which point with any degree of probability to this formula representing the constitution of the free amide. The primary amide structure is more correctly regarded as being a resonance hybrid of these extreme forms.

In the case of alkylated amides, numerous and stable representatives

corresponding to both types have been isolated. These derivatives are therefore structurally isomeric.



Alkylated acid amide



Imino-ether.

The names of the acid amides, according to the Geneva nomenclature, are obtained from those of the hydrocarbons from which they are derived by the addition of the termination " amide."

Formamide, *methanamide*, is a liquid which is readily soluble in water and alcohol. With mercuric oxide it yields a soluble salt, $(HCO.NH)_2Hg$, and on treatment with phosphorus pentoxide it gives hydrogen cyanide.

Acetamide, *ethanamide*, $CH_3.CO.NH_2$, forms long needles, m.p. 82° and b.p. 222°, readily soluble in water and alcohol. It is most simply prepared by the action of ammonia on ethyl acetate.

7. Amido-chlorides and Imido-chlorides

Amido-chlorides are produced by the action of phosphorus pentachloride on acid amides :—

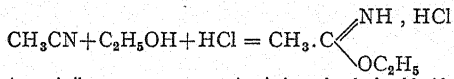
$$CH_3.CO.NH_2+PCl_5 = CH_3.CCl_2.NH_2+POCl_3$$

Unless the hydrogen of the amido group is substituted by alkyl radicals, these compounds are very unstable, a molecule of hydrogen chloride first splitting off to give the more stable imido-chlorides, which finally yield nitriles.

$$\underset{\text{Amido-chloride}}{CH_3.CCl_2.NH_2} \xrightarrow{-HCl} \underset{\text{Imido-chloride}}{CH_3.CCl:NH} \xrightarrow{-HCl} \underset{\text{Nitrile.}}{CH_3.C:N}$$

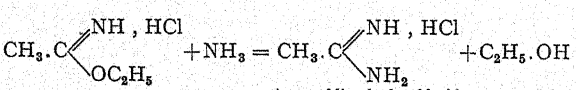
8. Imino-ethers and Amidines

As has already been mentioned, the *imino-ethers* are structurally isomeric with the alkylated acid amides. They are obtained in the form of hydrochlorides when carefully dried hydrochloric acid gas is led into a solution of a nitrile dissolved in the required alcohol.



Acetonitrile — Acetimino-ether hydrochloride.

Most of these salts crystallise well, but are decomposed by water to form ammonium chloride and an ester. The free imino-ethers are liberated from the salts by treatment with alkali. They are basic liquids of peculiar smell, which are very sparingly soluble in water. Their properties differ considerably from those of the isomeric substituted amides. If the hydrochloride of an imino-ether is treated with ammonia, an *amidine salt* is formed.



Acetamidine hydrochloride.

The amidines are strong monacid bases, which are unstable in the free state, decomposing rapidly into ammonia and a nitrile or acid amide. The free compounds are only stable when the hydrogen attached to the nitrogen atoms is partially or completely replaced by alkyl groups.

9. Acid Hydrazides and Acid Azides

These substances have been investigated more particularly by Curtius and his co-workers. The introduction of acid radicals into hydrazine results in the formation of monoacyl- or primary hydrazides, $R.CO.NH.NH_2$, and *sym.* diacyl- or secondary hydrazides, R.CO.NH.NH.CO.R.

Primary hydrazides are obtained by the action of hydrazine hydrate on esters, secondary *sym.* hydrazides being also formed as a by-product. The former are of a somewhat stronger basic character than acid amides and give well-defined salts. They are easily hydrolysed, and most of them reduce ammoniacal silver nitrate in the cold. Fehling's solution is only reduced on warming.

Acid azides are produced by the action of nitrous acid on primary hydrazides,

$$R.CO.NH.NH_2 + HONO = R.CON_3 + 2H_2O$$

or better by interaction of an acid chloride with sodium azide in a suitable solvent such as aqueous acetone.[1]

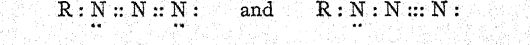
$$CH_3.COCl + NaN_3 = \underset{\text{Acetazide.}}{CH_3.CON_3} + NaCl$$

Acid azides dissolve in most organic solvents but are in general only sparingly soluble in water. In the solid state the compounds show marked differences in explosive properties. With acids and alkalis they are hydrolysed to hydrazoic acid and the parent organic acid, although some molecular rearrangement may also occur which is described in more detail below.

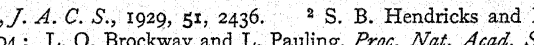
An interesting point in connection with the azides is that they offer a means of replacing the carboxyl group of an acid with the amino group, and thus of passing from an acid to an amine containing one carbon atom less. This process, known as the **Curtius rearrangement,** is carried out by decomposing the acid azide by heating it in a solvent. Nitrogen is evolved and the resulting organic radical rearranges itself into an isocyanate, which can in many cases be isolated. In aqueous solvents the isocyanate may suffer partial hydrolysis to amine, and this will react with unchanged isocyanate to form a substituted urea. Both isocyanate and urea, however, are converted into the amine during the final hydrolysis with hot mineral acid.

$$R.CON_3 \longrightarrow [R.CON] + N_2 \longrightarrow R.N:CO \longrightarrow R.NH_2 + CO_2$$

The structure of the azide group was originally represented by E. Fischer as cyclic, , and later by Angeli and Thiele as an open chain, —N : N ⋮ N. Although in the latter formula the electronic state of the central nitrogen, with five co-valent links, is not in accordance with modern theory, recent investigations of solid sodium and potassium azides by X-ray analysis [2] and of their solutions by Raman spectra have fully established an open chain structure. Considering the ease with which the azide ion is converted into an azide group united by a co-valent bond to carbon, and *vice versa,* it is probable that the same open structure is present in the acid azides. The difficulty presented by an individual formula of the type R—N=N→N or R—N←N≡N is that the presence of the co-ordinate link, indicated by an arrow, should correspond to a high dipole moment, whereas the values found are only of the order 1·55. At present an azide is best regarded as a resonance hybrid between these two forms.[3] In Pauling's nomenclature, in which the arrangement of the electrons is represented by dots, these forms are written respectively as



and



[1] See G. Powell, *J. A. C. S.*, 1929, **51**, 2436. [2] S. B. Hendricks and L. Pauling, *J. A. C. S.*, 1925, **47**, 2904; L. O. Brockway and L. Pauling, *Proc. Nat. Acad. Sci.*, 1933, **19**, 860. [3] For further details see N. V. Sidgwick, *The Organic Chemistry of Nitrogen* (revised by T. W. J. Taylor and W. Baker), Clarendon Press, 1937.

10. Aliphatic Nitriles or Alkyl Cyanides, R.C N

Nitriles are formed when acid amides are heated with a dehydrating agent (P_2O_5, P_2S_5, PCl_5), or when alkyl iodides, bromides or chlorides are heated with alcoholic potassium cyanide. The former method gave rise to the name of acid nitrile, *e.g.* acetonitrile, and the latter to that of alkyl cyanide, *e.g.* methyl cyanide.

$$CH_3I + KCN = CH_3.CN + KI$$

Acetonitrile or methyl cyanide.

Nitriles are also produced by the dry distillation of a mixture of potassium alkyl sulphate and potassium cyanide.

$$SO_2\langle^{OC_2H_5}_{OK} + KCN = C_2H_5.CN + K_2SO_4$$

Propionitrile or ethyl cyanide.

The nitriles are colourless liquids or crystalline solids with a peculiar and not unpleasant smell. The lower members are miscible with water, but the solubility diminishes with increasing molecular weight.

When warmed with acids or alkalis they take up two molecules of water to form fatty acids of the same number of carbon atoms, a change generally known as *hydrolysis*. Hence the carbon of the cyanogen group is directly united to a carbon atom of the alkyl radical.

$$CH_3.CN + 2H_2O = CH_3.COONH_4$$
$$CH_3.COONH_4 + KOH = CH_3.COOK + NH_3 + H_2O$$

Many reactions of the nitriles depend upon the ease with which the triple bond is converted into a double or single bond. These are to be classed as *addition reactions*.

Nascent hydrogen, for example, unites with nitriles to give primary amines (see p. 169). For other addition reactions compare pp. 177, 210 and 212.

Acetonitrile, methyl cyanide, $CH_3.CN$, is a pleasant-smelling liquid, b.p. 81°, which is usually prepared by heating acetamide with phosphorus pentoxide.

Nitro-acetonitrile, $NO_2.CH_2.CN$, is obtained by removing the elements of water from methazoic acid by means of thionyl chloride.[1] It is a yellow oil possessing a faint odour.

Isocyanides or Carbamines, R.NC

Isocyanides or carbamines are isomeric with the nitriles, from which they differ in having the nitrogen of the CN group linked directly to the alkyl radical. According to the earlier work of Nef,[2] the carbon of the isocyanide group was assumed to be divalent as in $R \cdot N{=}C$. Later determinations of the parachors of these compounds, however, indicate

[1] W. Steinkopf and L. Bohrmann, *Ber.*, 1908, **41**, 1044. [2] Nef, *Ann.*, 1892, **270**, 267.

that they contain a semi-polar double bond, leading to the structure $R \cdot N \rightleftharpoons C$ (see p. 88).

They are formed together with nitriles by heating potassium cyanide with alkyl iodides or with alkali salts of alkyl sulphuric acids, and constitute the main reaction product when an alkyl iodide is heated with cyanide of silver.

Isocyanides, free from admixed nitriles, may be obtained by warming primary amines with chloroform and caustic potash (see p. 133).

In their properties the isocyanides differ strongly from the nitriles. They are colourless liquids of extremely unpleasant odour. Towards alkalis they are comparatively stable, but on treatment with acids they decompose into a primary amine and formic acid. From this reaction it follows that the alkyl group is directly attached to nitrogen.

$$CH_3.NC + 2H_2O = CH_3.NH_2 + H.COOH$$

They yield unstable addition products with halogens and with hydrochloric acid, *e.g.* $2CH_3.NC, 3HCl$, and at high temperatures show a strong tendency to change into the isomeric nitriles.

II.—DERIVATIVES OF MONOCARBOXYLIC ACIDS FORMED BY SUBSTITUTION IN THE HYDROCARBON RADICAL

1. Halogen-substituted Acids

Halogen-substituted carboxylic acids are prepared in the same way as the corresponding derivatives of hydrocarbons. Substitution by chlorine or bromine takes place by the direct action of halogen on the acid, the degree of substitution depending on the duration of the reaction and other experimental conditions. The reaction proceeds slowly, but

$$CH_3.COOH + Cl_2 = CH_2Cl.COOH + HCl$$

may be accelerated in various ways, among others by the addition of a "carrier." Substitution by chlorine or bromine, for example, is assisted by the addition of a small amount of iodine.

If chlorine or bromine is allowed to react with a fatty acid in the presence of red phosphorus, the first step is the formation of an acid chloride or bromide. The latter then undergoes substitution, which takes place more readily than in the case of the free acid.

Bromination in the presence of red phosphorus (*Hell-Volhard-Zelinsky method*) is not only useful for the preparation of substitution products, but it often gives valuable information as to the constitution of the acid. It is found that the halogen under these conditions always replaces a hydrogen atom attached to the α-carbon atom. Propionic and butyric acids, for example, yield respectively,

$CH_3.CHBr.COOH$	and	$CH_3.CH_2.CHBr.COOH$
α-Bromo-propionic acid		α-Bromo-butyric acid

If no hydrogen is available in the α-position, as is the case with trimethyl-acetic acid $(CH_3)_3C.COOH$, then no substitution takes place at all under these conditions of experiment. This reaction, therefore,

provides a means of establishing the presence or absence of α-hydrogen atoms in a carboxylic acid.

Halogen-substituted acids can also be prepared by the direct addition of halogen or hydrogen halide to unsaturated acids, and by the action of phosphorus halides on hydroxy acids.

A convenient way of obtaining α-bromo-acids of the fatty series is to brominate the corresponding monoalkyl-malonic acids, $R.CH(COOH)_2$. Compounds of the general formula $R.CBr(COOH)_2$ are thus obtained in almost quantitative yield. When these are heated they lose carbon dioxide and are converted into brominated acids of the type $R.CHBr.COOH$.

Iodine-substituted acids are generally prepared from the corresponding chlorine or bromine compounds by heating with potassium iodide.

$$CH_2Cl.COOH + KI = CH_2I.COOH + KCl$$

Isomerism and Nomenclature.—Monochloro-acetic acid exists in one form only, but the mono-halogen derivatives of propionic acid and its higher homologues may occur in isomeric forms, according to the position of the halogen in the carbon chain. It is usual to indicate the position of a substituent by labelling the carbon atoms α, β, γ, δ, etc., starting with the atom adjacent to the carboxyl group.

$CH_3.CHBr.COOH$	$CH_2Br.CH_2.COOH$	$CH_2Br.CH_2.CH_2.COOH$
α-Bromo-propionic acid	β-Bromo-propionic acid	γ-Bromo-butyric acid.

Properties.—The halogenated fatty acids may be either liquids or solids. On the one hand they undergo the usual reactions of carboxylic acids in forming salts, esters, chlorides and anhydrides; on the other, they resemble the alkyl halides in the reactivity of the halogen, which can readily be exchanged for hydroxy, amino and other groups. Halogen-substituted acids are more strongly acidic than the parent compounds, the influence of the different halogens being in the order Cl > Br > I, and varying also with the number and position of the halogen atoms present. Thus monochloro-acetic acid is considerably stronger than acetic acid, and the strength increases still further in di- and trichloro-acetic acids (see p. 79).

The chemical properties of the substituted acids also vary considerably with the position of the halogen in the molecule, as may be seen from the following:

α-Halogenated acids on being boiled with alkalis, or in many cases merely with water, readily exchange the halogen atom for a hydroxyl group with the formation of an α-hydroxy acid.

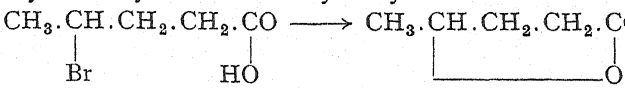
$$CH_2Cl.COOH + H_2O = \underset{\text{Hydroxy-acetic acid or glycollic acid.}}{CH_2(OH).COOH} + HCl$$

β-Halogenated acids, on the other hand, when heated with water lose hydrogen halide and yield unsaturated acids.

$$\underset{\text{β-Chloro-propionic acid}}{CH_2Cl.CH_2.COOH} = \underset{\text{Acrylic acid.}}{CH_2:CH.COOH} + HCl$$

γ-Halogenated acids under this treatment first form the corresponding

γ-hydroxy acids, which then by loss of water immediately pass into lactones or cyclic anhydrides of the hydroxy acids.[1]



Owing to their reactivity the halogenated acids are of great value in organic synthesis.

Monochloro-acetic acid, $CH_2Cl.COOH$, is prepared by passing chlorine into hot acetic acid in the presence of phosphorus. It crystallises in needles, m.p. 63°. The acid has a strong corrosive action on the skin, and therefore requires careful handling. *Dichloro-acetic acid*, $CHCl_2.COOH$, is best prepared by boiling chloral hydrate with aqueous sodium cyanide; and *trichloro-acetic acid*, $CCl_3.COOH$, by oxidation of chloral hydrate with nitric acid.

2. Esters of Nitroso- and Nitro-carboxylic Acids [2]

Preparation.—When the nitrous gases obtained by heating arsenious oxide with nitric acid are led into esters of acyl-substituted fatty acids in the absence of solvents, a reaction occurs which leads to the removal of the acyl group (CHO, $CO.CH_3$, $CO.C_6H_5$) and the formation of nitroso derivatives of the carboxylic esters.

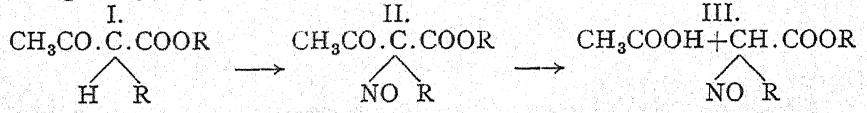
Omitting possible intermediate products, the reaction may be represented as follows:

where R represents an alkyl radical and Ac an acyl group.

For the preparation of nitroso-carboxylic esters on a larger scale it is best to start from the corresponding acetyl derivatives, as these are well known and can generally be obtained in quantity. Methyl-acetoacetic ester, for example, is the best starting-point in the preparation of methyl-nitroso-acetic ester.

Nitroso-carboxylic esters can also be prepared in a similar manner by the replacement of inorganic acyl substituents.

Finally, it should be noted that no replacement takes place when diethyl-acetoacetic ester is submitted to the action of nitrous gases. A necessary condition for interaction is that the carbon atom to which the acyl group is attached should also be united to an alkyl radical and a hydrogen atom. From this it may be concluded that the reaction probably takes place with the formation of an intermediate product, II, which then undergoes hydrolysis.



[1] Fittig, *Ber.*, 1894, **27**, 2658. A detailed description of the lactones is given later, see index.

[2] J. Schmidt and co-workers, *Ber.*, 1909, **42**, 497, 1886. *Ann.*, 1910, **377**, 23, 30; 1913, **398**, 251.

The *properties of nitroso-esters* are such as would be expected of true nitroso derivatives; they are blue or bluish-green oily liquids of pungent smell, which cannot be distilled without decomposition. A comparison of different alkylated nitroso-acetic esters shows that the shade of blue increases in depth as the alkyl group increases in size.

On allowing any of these compounds to stand for some time at the ordinary temperature, or more rapidly on shaking with water or alkalis, the characteristic blue colour disappears. This is partly due to intramolecular change in which the nitroso group is converted into an isonitroso group,

$$O:N-\underset{\dot{C}H_3}{\overset{H}{\dot{C}}}-COOC_2H_5 \longrightarrow HO.N:\underset{\dot{C}H_3}{C}-COOC_2H_5$$

and partly to polymerisation, as can be shown by molecular weight determinations.

Among other properties these compounds all give the Liebermann nitroso reaction. When heated with concentrated sulphuric acid and phenol and then dissolved in water, solutions are obtained which develop a blue or green colour on being made alkaline.

The constitution of the nitroso-compounds is proved on the one hand by their reduction to amino-esters, and on the other by their oxidation to the corresponding nitro-esters.

Esters of nitro-carboxylic acids are yellowish oils which require to be handled with great care, as they decompose on distillation and explode when rapidly heated.

Nitro-aliphatic Acids.—Nitro-acetic acid has been prepared by the action of potash on nitro-methane, methazoic acid being formed as an intermediate product. The potassium salt of nitro-acetic acid so obtained is then decomposed with dry hydrochloric acid.[1] *Nitro-acetic acid* is stable in the dry state and crystallises in needles, m.p. 87° to 89°. When heated in larger quantities an explosive decomposition may set in.

3. Amino-acids

Amino-acids are acids in which hydrogen of the hydrocarbon radical is replaced by the monovalent amino group —NH_2. They differ strongly from the corresponding acid amides, since the amino group resembles that in the amines in being firmly bound and unaffected by boiling alkalis. As in the case of the halogen acids (see p. 216), a distinction is made between α-, β-, γ-substituted acids, etc., according to the position of the substituent in the carbon chain.

$CH_3.\underset{}{\overset{NH_2}{\dot{C}H}}.COOH$ — α-Amino-propionic acid

$\underset{}{\overset{NH_2}{\dot{C}H_2}}.CH_2.COOH$ — β-Amino-propionic acid.

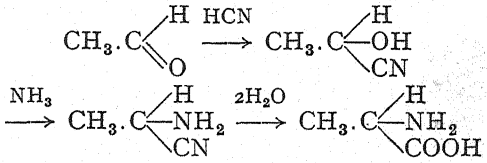
Physiological Importance of Amino-acids.—Investigation has shown that proteins are hydrolysed by acids or alkalis, or by the ferments in

[1] Steinkopf and co-workers, *Ber.*, 1909, **42**, 2026, 3925; 1910, **43**, 3239; 1911, **44**, 2891.

the digestive tracts, to yield proteoses, peptones and finally amino-acids. Of the numerous acids obtained in this manner, the constitution of the majority is now known and many have been obtained synthetically.

Monamino-acids may be prepared by the following methods.

1. Aldehydes and ketones when treated with hydrogen cyanide yield cyanhydrins. These with ammonia are converted into amino-nitriles, which on hydrolysis yield α-amino-acids (*Strecker*).



The first two phases of the above process may also be combined by treating an aldehyde or ketone directly with ammonium cyanide.

An even more convenient method of effecting this synthesis in the case of the sparingly soluble amino-acids [1] is to bring equimolecular proportions of potassium cyanide and ammonium chloride into reaction with the aldehyde or ketone, in aqueous or aqueous alcoholic solution.

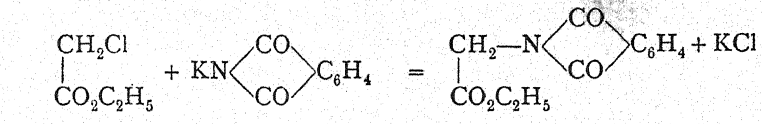
In this case the cyanide first undergoes hydrolytic dissociation to give hydrogen cyanide and potassium hydroxide, $KCN+H_2O=HCN+KOH$. The former combines with the aldehyde or ketone to yield the cyanhydrin, which is then transformed into the amino-nitrile by the action of ammonia liberated from the free alkali and ammonium chloride.

2. By treating halogen-substituted acids with ammonia.[2]

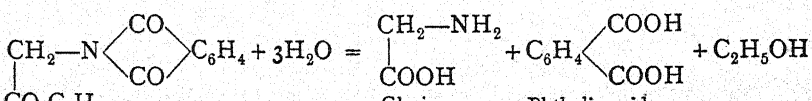
$$H_3N+Cl.CH_2.COOH = H_2N.CH_2.COOH+HCl$$

When this reaction is applied to the preparation of primary monamino-acids, the latter may react further with yet unchanged halogen acid to form secondary and tertiary amino-acids, such as $NH(CH_2.COOH)_2$ and $N(CH_2.COOH)_3$.

In order to avoid these by-reactions in the preparation of primary α-amino-acids potassium phthalimide may be used in place of ammonia (*Gabriel*). The pure amino-acid is then obtained from the product so formed by heating it to 200° with hydrochloric acid (see also p. 455).



Monochloro-acetic ester — Potassium phthalimide — Phthalyl-glycine ester.



Glycine — Phthalic acid.

[1] *Ber.*, 1906, **39**, 1722. W. Cocker and A. Lapworth, *J. C. S.*, 1931, 1391. [2] E. Fischer and Schmitz, *Ber.*, 1906, **39**, 351.

3. From ketonic or aldehydic acids (oxo-acids) by conversion into the oximes or hydrazones, followed by reduction, preferably by means of aluminium amalgam.

$CH_3.CO.COOH \longrightarrow CH_3.C(NOH).COOH \longrightarrow CH_3.CHNH_2.COOH$

Pyruvic acid — Oxime — α-Amino-propionic acid.

$CH_3—C(=N.NHC_6H_5)—COOH$

Phenyl-hydrazone.

The synthesis of α-amino-acids by the reduction of the corresponding oximes may be employed with advantage in all cases where the α-ketonic acid is easily prepared.[1] The catalytic reduction of a ketonic acid dissolved in aqueous or alcoholic ammonia also yields the corresponding amino-acid.[2]

Diamino-acids are in general more difficult to prepare than monamino-acids.

1. A modified form of the phthalimide method described above is available for the preparation of these compounds. Thus, for example, αδ-diamino-valeric acid may be synthesised from phthalimido-propyl-malonic ester, $C_6H_4(CO)_2N.CH_2.CH_2.CH_2.CH(COOC_2H_5)_2$. The latter readily forms a bromo-derivative, which after hydrolysis and splitting off carbon dioxide yields phthalimido-bromo-valeric acid, $C_6H_4:C_2O_2:N.CH_2.CH_2.CH_2.CHBr.COOH$. From this, by the action of ammonia and removal of the phthalyl radical, is obtained αδ-diamino-valeric acid, $NH_2.CH_2.CH_2.CH_2.CH(NH_2).COOH$, which is the racemic form of the naturally occurring ornithine [3] (see p. 227).

2. Diamino-acids are also formed by the action of ammonia on acids containing two ethylene bonds. Thus on heating sorbic acid with ammonia a diamino-caproic acid is produced.[4]

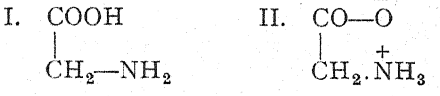
3. Amino-acids are largely prepared by hydrolysing proteins with mineral acid and separating the resulting mixture by Fischer's ester method (see p. 222). A further method of isolation has been described by *Dakin*.[5] It consists in removing the monamino-acids and proline by *continuous extraction with butyl alcohol*; the diamino-acids and the monamino dicarboxylic acids remain in the aqueous layer, from which they can be separated. This process has the advantage that optically active acids are not racemised.

Properties and Constitution of Amino-acids.—The majority of the amino-acids are crystalline compounds, often of sweet taste, which are soluble in water but insoluble in alcohol and ether.

They are both basic and acidic in character, and therefore form salts with acids as well as with bases. Simple monamino-acids are neutral

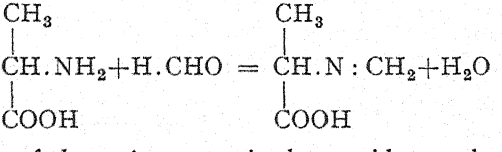
[1] Compare Knoop and Hoessli, *Ber.*, 1906, **39**, 1477. [2] Knoop and Österlin, *Z. physiol. Ch.*, 1925, **148**, 294. [3] E. Fischer, *Ber.*, 1901, **34**, 454. [4] E. Fischer and Schlotterbeck, *Ber.*, 1904, **37**, 2357. [5] *Biochem. J.*, 1918, **12**, 290.

in reaction, and it is assumed that the carboxyl and amino groups neutralise each other within the molecule to form an inner salt. According to the older view their properties were represented by the formula I (amino-acetic acid being used as an example), in which the amino and carboxyl groups are supposed to be free. According to modern ideas a compound of this type is unstable, as the amino group would have a strong tendency to react with the carboxyl group to form an ammonium salt. This involves the ionisation of the carboxyl group, leaving a negatively charged residue, and union of the proton with nitrogen, which acquires a positive charge. These views are expressed in II, which is known as the *betaine formula* for amino-acids.



Among other facts supporting this structure may be mentioned the existence and mode of formation of trimethyl-glycine or betaine (see p. 226). Nevertheless, formulæ of type I are more convenient for representing changes undergone by amino-acids and are in common use.

As amino-acids are neutral in reaction they cannot be directly titrated with alkalis. Use may be made of *Sörensen's formal titration method*, in which the basic amino group is modified by interaction with formaldehyde, giving a relatively strong acid which may be titrated in the usual way.



The *hydrogen of the amino group* in these acids may be replaced by an alkyl radical or by an acyl group. In the latter case the compound formed is both an acid amide and an amino-acid, *e.g.*,

$$R.CO.Cl+H_2N.CH_2.COOH = R.CO.NH.CH_2.COOH+HCl.$$

Prominent among compounds of this type are the benzoyl derivatives, which were employed by E. Fischer in resolving racemic amino-acids into their optically active components. Unlike the amino-acids, the benzoyl compounds are strongly acidic and can be combined with an optically active base. The mixture of salts thus formed from a racemic acid can then be separated by fractional crystallisation (*cf.* p. 38), and the active benzoyl compounds converted by hydrolysis into the active amino-acids.

The corresponding *compounds of amino-acids with β-naphthalene sulphonic acid* are distinguished by their small solubility in water, and are therefore useful for the isolation and identification of amino-acids.[1]

[1] E. Fischer and Bergell, *Ber.*, 1902, **35**, 3779.

Amino-acids unite with phenyl isocyanate to form *phenylureïdo-acids*,[1] *e.g.*,

$$C_6H_5NCO + H_2N.CH_2.COOH = C_6H_5.NH.CO.NH.CH_2.COOH$$

Phenyl isocyanate — Amino-acetic acid — Phenylureïdo-acetic acid.

Owing to their low solubility these compounds and the corresponding substances formed with α-naphthyl-isocyanate, $C_{10}H_7NCO$, are also used in the separation of amino-acids.[2]

In the case of diamino-acids the best means of separation is *precipitation with phosphotungstic acid.*

Most amino-acids yield a sparingly soluble *copper salt.*

Esters of amino-acids may be prepared by leading hydrochloric acid gas into a solution of the acid in absolute alcohol. The hydrochlorides so formed (*e.g.* HCl, $NH_2.CH_2.COOC_2H_5$) are decomposed with concentrated alkali at a low temperature and the free ester, ($NH_2.CH_2.COOC_2H_5$), extracted with ether.[3]

Owing to their property of distilling without decomposition, the esters are of great service in separating the mixtures of amino-acids produced by the hydrolysis of proteins (*Fischer*). Amino-esters are exclusively basic in character, and in their reactions strongly resemble primary amines. They yield acid amides on treatment with liquid ammonia, and as is described in more detail below, can be converted into *diketo-piperazines.*

The *chlorides of amino-acids*, containing the group .COCl in place of carboxyl, are, according to Fischer,[4] best prepared by shaking the acid at 0° to 20° with about 10 to 15 times the theoretical amount of acetyl chloride and the calculated amount of phosphorus pentachloride. Under these conditions the hydrochloride of the acid chloride is obtained, of the general formula $\begin{matrix} R.CH.COCl. \\ | \\ NH_3Cl \end{matrix}$ Compounds of this type possess the reactivity of ordinary acid chlorides and, as will be seen later, may be used in the synthesis of polypeptides.

Action of Yeast and Moulds on Amino-acids.—It has already been stated on p. 152 that fermenting yeast in the presence of sugar converts amino-acids into alcohols, and that this process can be used for preparing alcohols from amino-acids. Certain moulds, such as *oidium lactis*, effect the removal of the ammonia required as nutriment in a somewhat different manner[5] without elimination of carbon dioxide, according to the equation

$$R.CH(NH_2).CO_2H + H_2O = R.CH(OH).CO_2H + NH_3$$

During the growth of the fungus the chain of carbon atoms remains

[1] Paal, *Ber.*, 1894, **27**, 974. [2] Neuberg and Manasse, *Ber.*, 1905, **38**, 2359. [3] E. Fischer, *Ber.*, 1901, **34**, 433. In place of potassium hydrate, lead hydroxide may conveniently be used (*Z. physiol. Ch.*, 1911, **73**, 459). [4] E. Fischer, *Ber.*, 1906, **39**, 545. [5] F. Ehrlich, *Ber.*, 1911, **44**, 139, 888.

practically unaltered, and an almost quantitative yield of α-hydroxy acid can be isolated from the solution. In this case only very small amounts of alcohol are produced. Since any desired quantity of an amino-acid may be transformed in a comparatively short time by means of *oidium lactis*, we have here a convenient way of preparing optically active hydroxy-acids from active or racemic amino-acids, a method which has many advantages over purely chemical processes.

The *bacterial fermentation of amino-acids*, which takes place in the intestinal canal, leads to a variety of products including phenols, mono- and di-amines and fatty acids. The connection between these compounds and particular amino-acids can usually be deduced from the constitution of the latter, and has in many cases been proved experimentally.

The *degradation of the amino-acids by animal cells* occurs by way of decarboxylation or by oxidative de-amination, amides or ketonic acids being thus formed as intermediate products.

By application of the *Grignard reaction to amino-esters* it is possible to obtain amino-alcohols.[1]

As in the case of the halogenated acids (p. 216), the chemical behaviour of amino-acids varies with the position of the amino group in the carbon chain.

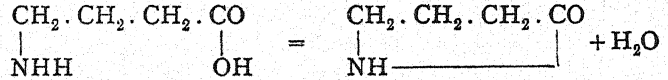
α-*Amino-acids* readily lose two molecules of water from two molecules of acid, or two molecules of alcohol may be eliminated from two molecules of amino-ester, to form cyclic anhydrides called 2 : 5-*diketo-piperazines*. These possess the properties of acid amides.[2]

Glycine anhydride,
2 : 5-diketo-piperazine.

β-*Amino-acids* readily part with ammonia to yield *unsaturated acids*.

β-Amino-propionic acid — Acrylic acid.

γ *and* δ-*amino-acids*, and those with longer chains, are easily converted by loss of water into inner anhydrides termed *lactams*. These are cyclic acid amides which correspond to the lactones or cyclic anhydrides of hydroxy acids.

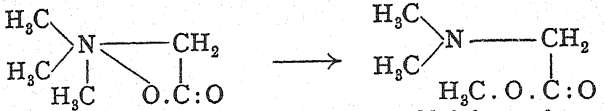


γ-Amino-butyric acid — γ-Butyro-lactam or pyrrolidone.

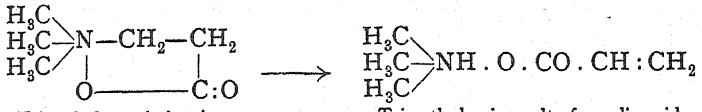
A comparison of the behaviour of the completely alkylated compounds, known as betaines, under the influence of heat, shows even more clearly how the position of the amino group affects the properties. α-Betaines on fusion are converted smoothly into esters of tertiary amino-acids (I); the simplest β-betaine, propio-betaine, isomerises to form the trimethylamine

[1] Paal and Weidenkaff, *Ber.*, 1906, **39**, 810. [2] E. Fischer, *Ber.*, 1906, **39**, 556.

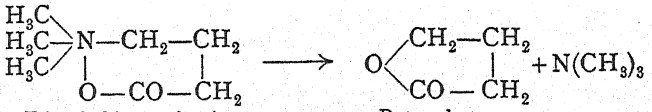
salt of acrylic acid (II); and butyro-betaine, a γ-betaine, decomposes into butyro-lactone and trimethylamine (III).

I. 

Betaine — Methyl ester of dimethylamino-acetic acid.

II. 

Trimethyl-propio-betaine — Trimethylamine salt of acrylic acid.

III. 

γ-Trimethyl-butyro-betaine — Butyro-lactone.

Action of Sodium Hypochlorite on α-Amino-acids.[1]—Hypochlorites react with α-amino-acids in the same way as with simple amines. According to the amount of hypochlorite employed, and the number of hydrogen atoms directly attached to nitrogen, there are formed mono- or dichloro-substitution products. Further action results in oxidation and the formation of an aldehyde containing one atom of carbon less than the original acid, *e.g.*,

$$CH_3.CH(NH_2).COOH \longrightarrow CH_3.CHO.$$

Glycine, glycocoll, *amino-acetic acid, amino-ethane acid* $\begin{matrix}COOH\\|\\CH_2.NH_2\end{matrix}$

or $\begin{matrix}CO.O\\|\quad\quad|\\CH_2.NH_3\end{matrix}$, melts at 232° to 236°, and is formed by the general methods already described. It may be prepared by boiling glue with dilute sulphuric acid or baryta (hence its name); also from its benzoyl derivative *hippuric acid*, which occurs in the urine of horses, by hydrolysis with hydrochloric acid.

$C_6H_5.CO.NH.CH_2.COOH + H_2O + HCl$
Hippuric acid or benzoyl-glycine

$= HCl, NH_2.CH_2.COOH + C_6H_5.COOH$
Glycine hydrochloride · Benzoic acid.

When benzoic acid is introduced into the human organism it also becomes condensed with glycine and eliminated in the urine as hippuric acid. Similarly, phenylacetic acid is removed from the animal organism in the form of *phenaceturic acid*, $C_6H_5.CH_2.CO.NH.CH_2.COOH$. It is believed that such changes are part of the natural process by which foreign substances are rendered harmless and removed from the system. In birds, ornithine (p. 227) plays the part of glycine in the above reactions, benzoic acid being eliminated as *ornithuric acid* (dibenzoyl ornithine).

Glycine forms large rhombic crystals, dissolves easily in water and is insoluble in alcohol and ether. It possesses a sweet taste, and gives

[1] K Langheld, *Ber.*, 1909, **42**, 392, 2360.

a characteristic dark blue crystalline *copper salt*, of the composition $(NH_2.CH_2.COO)_2Cu+H_2O$. The latter is readily soluble in water and is formed when a solution of glycine is boiled with copper carbonate. The *ethyl ester* boils at 51·5° to 52·5° under 10 mm., and when reduced in neutral solution by means of sodium amalgam yields amino-acetaldehyde.[1]

Aliphatic Diazo-compounds.—Nitrous acid interacts with glycine ester to give diazo-compounds which are acid derivatives of diazo-methane (p. 174). The hydrochloride of glycine ester when treated with sodium nitrite yields **diazoacetic ester**, b.p. 140° under 720 mm. The latter is a yellow oil which is insoluble in water.

$$C_2H_5OOC.CH_2.NH_2,HCl+NaNO_2 = \underset{\text{Diazoacetic ester.}}{C_2H_5OOC.CHN_2}+NaCl+2H_2O$$

Diazo-compounds of analogous constitution are also formed by the action of nitrous acid on other amino-esters.[2]

Investigation has shown that only esters of α-amino acids can be converted into diazo-esters. No diazo-compounds have been isolated from free amino-acids or from esters of β- or γ-amino-acids. In addition, it is necessary that at least one hydrogen atom should be united to the α-carbon atom in order to permit the formation of two molecules of water on reaction with nitrous acid. The most stable diazo-compounds are obtained from substances such as glycine ester, which contain the group $—CH_2.NH_2$, and thus form derivatives in which a hydrogen atom still remains attached to the α-carbon atom.

Aliphatic diazo-esters are very reactive, nitrogen being readily eliminated and its place taken by two monovalent atoms or groups.

A point of special interest is the use of diazoacetic ester in the preparation of *diamide* or *hydrazine*, $NH_2.NH_2$, and the conversion of the latter into *hydrazoic acid*, N_3H (*Curtius*); also the synthesis of pyrazole-derivatives (see index) from the same starting material.[3] On reduction, diazoacetic ester is converted into hydrazino-acetic ester,[4] $NH_2.NH.CH_2.COOC_2H_5$.

Recently the poly-glycine esters (p. 229) have also been converted into diazo-esters (Curtius), *e.g.*,

$$\underset{\text{Glycyl-glycine ester}}{H_2NCH_2CO.NHCH_2CO_2C_2H_5} \longrightarrow \underset{\text{Diazo-acetylamino-acetic ester.}}{N_2:CHCO.NHCH_2CO_2C_2H_5}$$

These compounds undergo the same reactions as diazoacetic ester, and are therefore valuable in synthesis.[5]

The diazo-group in these esters was formerly believed to have the cyclic structure $—CH\begin{cases}N\\ \|\\ N\end{cases}$. Later evidence suggests that carbon and the two nitrogen atoms have a linear arrangement, and that we are here dealing with a case of mesomerism resembling that of diazomethane (see p 174).

[1] E. Fischer, *Ber.*, 1908, **41**, 1019. C. Neuberg, *ibid.*, 956. [2] See Curtius: "Ueber Hydrazin, Stickstoffwasserstoff und die Diazoverbindungen der Fettreihe," *Ber.*, 1896, **29**, 759. Curtius and Müller: "Neue Untersuchungen über Diazo-fettsäureester," *Ber.*, 1904, **37**, 1261. For isodiazoacetic ester see Hantzsch and Lehmann, *Ber.*, 1901, **34**, 2506; and for the polymerisation products of diazoacetic ester, Hantszch and Silberrad, *Ber.*, 1900, **33**, 58. [3] E. Buchner, *Ann.*, 1887, **237**, 214. [4] Darapsky and Prabhakar, *Ber.*, 1912, **45**, 1654, 2617. [5] Curtius and co-workers, *Ber.*, 1904, **37**, 1261; 1906, **39**, 1373.

Methyl-glycine, *sarcosine*, $\begin{matrix}COOH\\|\\CH_2.NH.CH_3\end{matrix}$ or $\begin{matrix}CO.\bar{O}\\|\\CH_2.\overset{+}{N}H_2.CH_3,\end{matrix}$ is formed from *creatine* (see p. 340), $\begin{matrix}COOH\\|\\CH_2.N(CH_3).C=NH\end{matrix}$ $\begin{matrix}\\|\\NH_2\end{matrix}$, which is present in meat juice, or from the alkaloid *caffeine* by warming with baryta water. Synthetically it may be prepared by the action of methylamine on chloroacetic acid. It melts at 210°, dissolves readily in water and sparingly in alcohol. With cyanamide it combines to form creatine.

Trimethyl-glycine, betaine, $\begin{matrix}CO.\bar{O}\\|\\CH_2.\overset{+}{N}(CH_3)_3\end{matrix}$, is present in cotton-seed, in the embryo of wheat and barley, and in the sugar beet. In the manufacture of sugar from the last source the betaine collects in the molasses. Betaine is formed by the oxidation of choline and may be obtained synthetically from trimethylamine and chloroacetic acid.[1] These methods of preparation confirm the above formula. All compounds of similar constitution, *i.e.* all internal salts of ammonium bases, are known under the general name of betaines (see p. 221).

Betaine crystallises in large crystals containing one molecule of water, which may be removed over sulphuric acid or at 100°. The anhydrous compound melts at 293°, being transformed into the *methyl ester of dimethyl-amino-acetic acid*,[2] and on further heating decomposes with formation of trimethylamine. On the technical scale trimethylamine is prepared by heating the molasses from beet sugar. Betaine can also be converted into glycollic acid by heating with caustic soda, or by the action of certain moulds.[3]

Alanine, *α-amino-propionic acid*, $CH_3.CH(NH_2).COOH$, which only occurs in the *d*-form in nature, is obtained from α-chloro- or α-bromo-propionic acid and ammonia. On treatment with nitrous acid it is converted into lactic acid (p. 235). Transitions between alanine and lactic acid have also been detected in the animal organism. These changes are of interest because they established for the first time an undoubted connection between a lower degradation product of proteins and a simple product of carbohydrate metabolism. Natural dextro-rotatory alanine is best prepared by the hydrolysis of silk. Owing to its relationship to *l*-glyceric aldehyde (adopted as a standard in determining the configuration of sugars and optically active acids) the natural alanine is more correctly described as *l*(+)-alanine [4] (compare sugars, p. 290).

***l*-Leucine,** *α-amino-isobutyl-acetic acid*, *α-amino-isocaproic acid*, $(CH_3)_2CH.CH_2.CH(NH_2)COOH$, occurs in the pancreas and spleen, and is formed in considerable quantity when proteins are decomposed with acids or alkalis, or by putrefaction. It can be prepared from horn or casein by heating with dilute sulphuric acid, forming a white crystalline product, m.p. 270°, which is optically active. Leucine and its pale blue

[1] Willstätter, *Ber.*, 1902, **35**, 603. [2] Willstätter, *Ber.*, 1902, **35**, 603. [3] F. Ehrlich and Lange, *Ber.*, 1913, **46**, 2746. [4] Freudenberg and Rhino, *Ber.*, 1924, **57**, 1547.

copper salt are both sparingly soluble in water. The inactive form may be prepared by interaction of isovaleraldehyde, ammonia, and hydrogen cyanide; by hydrolysis of the condensation product of isobutyraldehyde and hippuric acid [1]; or by reduction of α-oximino-isobutyl-acetic ester with sodium amalgam.

$$(CH_3)_2CHCH_2CH:O \xrightarrow{NH_4.CN}$$

Isovaleraldehyde

$$(CH_3)_2CHCH_2CH(NH_2)COOH \xleftarrow{\text{Reduction}} (CH_3)_2CHCH_2C(=NOH)COOC_2H_5$$

r-Leucine — α-Oximino-isobutyl-acetic ester.

***d*-Isoleucine,** *α-amino-β-methyl-β-ethyl-propionic acid*, $(CH_3)(C_2H_5)CH.CH(NH_2)COOH$, is found in nature associated with leucine, which it strongly resembles. It may be obtained from the strontium liquors used in refining sugar and by various synthetic methods. A simple method of preparation is from malonic ester and secondary butyl iodide in the following stages:

$$C_2H_5.CHI.CH_3 + CHNa(CO_2C_2H_5)_2 \longrightarrow C_2H_5.CH(CH_3).CH(CO_2C_2H_5)_2 \longrightarrow$$
$$C_2H_5.CH(CH_3).CH(CO_2H)_2 \longrightarrow C_2H_5.CH(CH_3).CBr(CO_2H)_2 \longrightarrow$$
$$C_2H_5.CH(CH_3).CHBr.CO_2H \longrightarrow C_2H_5.CH(CH_3).CH(NH_2).CO_2H$$

δ-Amino-n-valeric acid, $NH_2.CH_2.(CH_2)_3COOH$, m.p. 158°, has been isolated from the products of putrefaction of fibrin and flesh.

In addition to these monamino-acids, the majority of albuminous substances also contain varying amounts of **diamino acids.** According to Kossel, the latter predominate in the protamines. Examples of this type are ornithine, lysine and arginine.

The diamino-acids are distinguished from the monamino-acids by their alkaline reaction, resulting from the amino group which is not neutralised by intramolecular union. On putrefaction they undergo decarboxylation to yield diamines such as putrescine and cadaverine (p. 247).

Ornithine, *αδ-diamino-valeric acid*, $H_2N.CH_2.CH_2.CH_2.CH(NH_2)COOH$, was first obtained by the hydrolysis of its dibenzoyl compound *ornithuric acid*, which occurs in the excrement of hens fed with benzoic acid (see p. 224). The product so obtained is optically active. The racemic form of ornithine has been synthesised by E. Fischer [2] according to method 2 on p. 220, and resolved into its optically active components by Sörensen by way of the dibenzoyl compound.

Arginine, *α-amino-δ-guanido-valeric acid*,

$$HN=C(NH_2).NH.CH_2.CH_2.CH_2.CH(NH_2)COOH$$

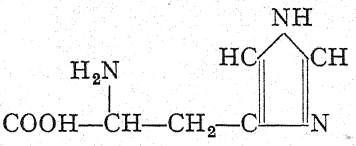
is found among the hydrolytic products of many animal proteins and is also contained in the cotyledons of etiolated lupins. It is closely related to ornithine, since on hydrolysis with barium hydroxide or by the action

[1] E. Erlenmeyer, jun., and Kunlin, *Ann.*, 1901, **316**, 145. [2] E. Fischer, *Ber.*, 1901, **34**, 454. Fischer and Zemplén, *Ber.*, 1909, **42**, 1022.

of the enzyme *arginase* it yields a mixture of ornithine and urea. Arginine has been synthesised by the combination of cyanamide, $CN.NH_2$, and ornithine.[1] It is usually prepared from the protein edestin by hydrolysis with fuming hydrochloric acid.

Lysine, *αε-diamino-caproic acid*, $NH_2.CH_2(CH_2)_3.CH(NH_2)COOH$, was discovered by Drechsel as a hydrolytic product of casein, and has been found by other workers among the products of acid hydrolysis of all proteins subsequently examined. The compound so obtained is dextro-rotatory. Pancreatic decomposition converts it into penta-methylene-diamine or cadaverine, $NH_2.CH_2(CH_2)_3CH_2.NH_2$. Fischer and Weigert prepared the racemic form of lysine by reducing α-oximino-γ-cyano-valeric acid.

Histidine is also a common decomposition product of proteins, and is an *α-amino-β-iminazyl-propionic acid* of the formula



It has been synthesised by Pyman.[2]

Hydroxy-, thio-, dibasic and cyclic amino-acids are described under their appropriate headings.

POLYPEPTIDES

It has already been stated that amino-acids predominate among the hydrolytic products of proteins, and for a long time attempts were made by various investigators to bring these again into combination by anhydride formation, with the object of building up larger molecules. The results obtained, however, were not satisfactory.

Emil Fischer was the first to develop methods by which the molecules of various amino-acids could be successively linked on to one another in a species of amide formation, each intermediate substance being isolated and identified. The resulting products, whose simplest representative is *glycyl-glycine*, $NH_2.CH_2.CO.NH.CH_2.COOH$, obtained from glycine, were described under the collective name of polypeptides. According to the number of amino-acid residues contained in the molecule, they are distinguished as *di-*, *tri-*, *tetrapeptides*, and so on.

In connection with these compounds Fischer writes: "The higher members of this synthetic series are, with respect to their external properties, certain colour reactions, and behaviour towards acids, alkalis, and ferments, so similar to the natural peptones that they may be considered as their nearest relatives, and I regard their synthesis as the first step in the production of natural peptones and albumoses."

[1] E. Schulze and E. Winterstein, *Ber.*, 1899, **32**, 3191. For the synthesis of arginine from ornithuric acid *cf.* Sörensen and M. Höyrup, *Ber.*, 1910, **43**, 643. [2] Pyman, *J. C. S.*, 1916, **109**, 186.

Synthesis of Polypeptides [1]

1. *Dipeptides* can be prepared by the hydrolysis of 2 : 5-diketo-piperazines. As stated on p. 223, the latter are obtained from α-amino-acids by loss of 2 mols. water, or from the corresponding esters by loss of 2 mols. alcohol.

Glycine anhydride, the simplest 2 : 5-diketo-piperazine, formed the starting-point of Fischer's investigations. When this compound is boiled for a short time with concentrated hydrochloric acid or shaken with cold dilute alkali, the ring is opened up and a hydrochloride or salt of glycyl-glycine is obtained.

$$\begin{array}{l} HN.CH_2.CO \\ \quad | \qquad | \\ OC.CH_2.NH \end{array} + H_2O = H_2N.CH_2.CO.NH.CH_2.COOH$$

2 : 5-Diketo-piperazine, glycine anhydride.[2] — Glycyl-glycine.

By using alcoholic hydrochloric acid in place of aqueous acid the 2 : 5-diketo-piperazine may be converted directly into *glycyl-glycine ester*, $NH_2.CH_2.CO.NH.CH_2.COOC_2H_5$.

2. More complex compounds can in many cases be prepared by elimination of one molecule of alcohol from two molecules of amino-esters or esters of higher polypeptides.[3] For example, the methyl ester of diglycyl-glycine at 100° quickly reacts according to the equation

$$2NH_2CH_2CO.NHCH_2CO.NHCH_2CO_2CH_3 = CH_3OH + NH_2CH_2CO.(NHCH_2CO)_4.NHCH_2CO_2CH_3$$

to form the methyl ester of a *hexapeptide*, from which the hexapeptide itself may be obtained by hydrolysis.

3. *Dipeptides* are obtained by bringing amino-acids or their esters into reaction with halogen-substituted acid chlorides, and treating the product with ammonia. For example, chloro-acetyl chloride $ClCH_2.COCl$ reacts with glycine to give *chloro-acetyl-glycine*, which with ammonia yields *glycyl-glycine*.

$$Cl.CH_2.CO.NH.CH_2.COOH + 2NH_3 = NH_2.CH_2.CO.NH.CH_2.COOH + NH_4Cl$$

Chloro-acetyl-glycine — Glycyl-glycine.

Glycyl-glycine may be once again combined with chloro-acetyl chloride and the product treated with ammonia, when *diglycyl-glycine* is obtained :—

$$H_2NCH_2CO.NHCH_2CO.NHCH_2COOH$$

Diglycyl-glycine.

This synthesis has been continued to the stage of a *pentapeptide* and could probably be carried on still further. Most of the polypeptides at present known have been obtained by this method, since it is possible

[1] For full details reference should be made to the lecture by Emil Fischer : " Untersuchungen über Aminosäuren, Polypeptide und Proteïne," *Ber.*, 1906, **39**, 530. See also Curtius, *J. pr. Ch.*, 1904 (2), **70**, 57. [2] With reference to an anhydride of glycine which is not 2 : 5-diketo-piperazine see H. Leuchs, *Ber.*, 1906, **39**, 857. [3] Curtius, *Ber.*, 1904, **37**, 1300.

to employ as components a variety of substituted acid chlorides on the one hand and on the other ordinary amino-acids, hydroxy-amino-acids (see index), and still more complicated substances, such as cystine.

4. The amino-acid chain may also be extended on the side of the carboxyl group. When amino-acids are shaken with acetyl chloride and phosphorus pentachloride, they are converted into hydrochlorides of the corresponding amino-acid chlorides (p. 222), which readily couple up with esters of amino-acids or polypeptides. Thus the chloride of α-bromo-isocaproyl-glycine reacts with glycine ester according to the following equation :—

$$C_4H_9.CHBr.CO.NH.CH_2.CO.Cl + 2NH_2.CH_2.CO_2C_2H_5$$
$$= HClNH_2.CH_2.CO_2C_2H_5 + C_4H_9.CHBr.CO.NH.CH_2.CO.NH.CH_2CO_2C_2H_5$$

By hydrolysis of the ester so obtained and subsequent treatment with ammonia it is converted into *leucyl-glycyl-glycine*.

This method is of special importance in its application to optically active amino-acids, whereby optically active polypeptides are produced. Such compounds are of particular interest because the naturally occurring proteins as well as their products of hydrolysis—albumoses, peptones, etc.—are also active. The methods just described were first applied to monamino-acids, and with the exception of the fourth, have also been extended to diamino- and hydroxy-amino-acids.

5. A novel method has recently been devised by Bergman [1] which offers the special advantages of ease of purification, high yields and absence of racemisation when dealing with optically active amino-acids. In this process the acid chloride of benzyl carbonic acid, prepared from benzyl alcohol and phosgene, is brought into reaction with the amino-acid. A benzyl-carbonato amino-acid is thus formed

$$C_6H_5.CH_2OH + Cl.CO.Cl \longrightarrow C_6H_5.CH_2.O.CO.Cl$$
$$C_6H_5.CH_2.O.CO.Cl + H_2N.CHR.COOH \longrightarrow C_6H_5.CH_2.O.CO.NH.CHR.COOH$$

which may be readily converted into its acid chloride and condensed with other amino-acid residues. The benzyl-carbonato peptides so obtained are crystalline and easily purified, and the protective grouping can be removed without difficulty by catalytic hydrogenation in the presence of platinum black. Under this treatment toluene is formed and the resulting carboxy-amino derivative loses carbon dioxide spontaneously to give the free peptide in almost quantitative yield.

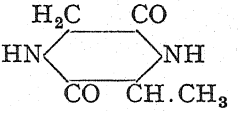
$$C_6H_5.CH_2.O.CO.NH.CHR.CO..... \longrightarrow C_6H_5.CH_3 + CO_2 + NH_2.CHR.CO.....$$

In his researches on the polypeptides Fischer finally succeeded in 1907 in building up an *octadekapeptide* containing fifteen glycine and three leucine residues, thus effecting the synthesis of the most complex organic substance whose constitution was then known. In its general

[1] M. Bergman, *Nature*, 1933, **131**, 662.

properties this polypeptide of molecular weight 1213 shows the greatest similarity to many naturally occurring proteins. Nine years later E. Abderhalden carried the synthesis a step further, and by the same method prepared a peptide with 19 amino-acid residues, containing one leucine residue more than Fischer's octadekapeptide. Some idea of the complexity of these substances may be gained from the fact that according to Fischer's calculations 816 isomeric octadekapeptides of the same composition are possible. For the polypeptide obtained by Abderhalden the number of isomerides has increased to 3876.

A discovery of some importance was the isolation in considerable quantity of a *methyl-diketo-piperazine*,



from the products of hydrolysis of silk fibroin,[1] which is identical with the synthetic compound from glycine and *d*-alanine. This diketo-piperazine corresponds to the two dipeptides *glycyl-alanine* and *alanyl-glycine*. Glycyl-*d*-alanine is the first recorded instance of a common link between polypeptide synthesis and protein disruption. It was isolated from the products of hydrolysis in the form of the α-naphthalene-sulphonic derivative and its structure confirmed by hydrolysing the latter to alanine and naphthalene-sulphoglycine. This reaction illustrates the utility of the naphthalene sulphonic derivatives in determining the structure of polypeptides.

d-*Alanyl*-l-*leucine* has been found among the hydrolytic products of elastin, and l-*leucyl*-d-*glutamic acid* among those of gliadin.

Glycyl-proline anhydride was discovered by Levene and Beatty among the products of digestion of gelatin, and Osborne and Clapp, by hydrolysing gliadin with hot sulphuric acid, observed the formation of a dipeptide of phenyl-alanine and proline. Dakin [2] has obtained an *isoleucyl-valine-anhydride* from the hydrolysis products of caseinogen. Fischer and Abderhalden also succeeded in preparing from silk fibroin a *tetrapeptide* composed of two glycine residues united with a *d*-alanine and an *l*-tyrosine residue. This compound already shows great similarity to the albumoses. An examination of the synthetic pentapeptide l-*leucyl-triglycyl*-l-*tyrosine* proved it to possess all the characteristics of the albumoses, hence it is to be assumed that the latter are by no means as complex as has hitherto been supposed.

A compound of special interest is the tripeptide *glutathione* isolated by Hopkins [3] and shown to be present in the majority of animal cells. It is built up of the three amino-acids, glycine, glutamic acid (p. 286) and cysteine. This tripeptide appears to function as an oxygen carrier,

[1] E. Fischer and Abderhalden, *Ber.*, 1906, **39**, 752; 1907, **40**, 3544. [2] Dakin, *Biochem. J.*, 1918, **12**, 290. [3] Hopkins, *Nature*, 1929, 445; Hunter and Eagles, *J. Biol. Chem.*, 1927, **72**, 147.

the mercaptan group in the cysteine unit readily becoming oxidised to a disulphide, which may again be reduced to give glutathione (compare cysteine and cystine, p. 241).

Properties of the Polypeptides

The polypeptides are solid substances which generally dissolve readily in water and very sparingly in alcohol. Mixed polypeptides as a rule dissolve more easily in water than those built up from the same amino-acid radical. The majority of the members of this group melt with decomposition at a temperature above 200°. Whereas most of the α-amino-acids have a sweet taste, the polypeptides are slightly bitter (or insipid), therein resembling the natural peptones. The higher polypeptides from the tripeptides upwards are precipitated by phosphotungstic acid in sulphuric acid solution, the precipitates being generally soluble in excess of the reagent. All the ordinary polypeptides immediately develop a blue or bluish-violet colour on being boiled in aqueous solution with precipitated copper oxide. A number of them also show the biuret reaction.[1]

The amino and carboxyl groups in the polypeptides are capable of undergoing the same reactions as in the amino-acids. Thus the polyglycine esters yield diazo-esters on treatment with nitrous acid :—

$$\underset{\text{Glycyl-glycine ester}}{H_2NCH_2CO.NHCH_2CO_2C_2H_5} \xrightarrow{HNO_2} \underset{\text{Diazo-acetylamino-acetic ester.}}{N_2:CHCO.NHCH_2CO_2C_2H_5}$$

Since these show the same reactivity as diazoacetic ester (p. 225), the azo group being readily exchanged for a variety of other atoms and groups, they may prove of no small importance in the future for the preparation of polypeptide derivatives.

Esters of polypeptides are much more easily purified and identified than the parent compounds, and may be used for the synthesis of more complex polypeptides. They may be prepared just as readily as those of the amino-acids by the use of alcoholic hydrochloric acid. Esters of the dipeptides are comparatively easily converted into diketo-piperazines (see p. 223) on treatment with alcoholic ammonia.

The *structure of polypeptides* may be deduced from the behaviour of the compounds formed with naphthalene-sulphonic chloride. When these are heated with moderately dilute hydrochloric acid the polypeptide chain is disrupted while the more stable link between the naphthalene-sulphonic group and the amino-acid remains fast, *e.g.*,

$$C_{10}H_7.SO_2.NH.CH_2.CO.NH.CH(CH_3).COOH + H_2O$$
$$= C_{10}H_7.SO_2.NH.CH_2.COOH + NH_2.CH(CH_3).COOH$$

From the examination of more complex polypeptides it appears that this is a general method for identifying the amino-acid attached to the beginning of the chain.

[1] The biuret reaction, which is characteristic of the natural peptones, consists in adding to the substance under investigation a sufficient quantity of sodium hydroxide and a few drops of dilute copper sulphate solution. The natural proteins give a blue to reddish-violet colour, and the albumoses and peptones a redder tint.

Synthetic polypeptides may be hydrolysed in much the same way as peptones or proteins. On boiling with concentrated hydrochloric acid they are completely decomposed into amino-acids, but alkalis only attack them slowly, particularly at the ordinary temperature.

The behaviour of polypeptides towards the digestive ferments, and above all towards the pancreatic secretions, is of special interest. Fischer and Abderhalden [1] found that the action of the pancreatic juices depends partly on the nature of the amino-acids present and partly on their arrangement. It thus varies with the length of the chain and in a high degree with the configuration of the molecule. In general, only those complexes are hydrolysed which are built up from optically active amino-acids occurring in nature. On the other hand, a number of artificial polypeptides have been tested with gastric juices without any hydrolysis having been observed.

Biological confirmation of the albuminous nature of polypeptides has also been supplied by directly feeding them to dogs. It was found that peptides resembled proteins in being degraded in the animal organism to simple amino-acids.[2]

4. Hydroxy-acids of the Aliphatic Series

Nomenclature.—The hydroxy-acids are derived from the fatty acids by replacing a hydrogen atom of the hydrocarbon radical by a hydroxyl group. They are generally designated by prefixing "hydroxy" to the name of the corresponding fatty acid. According to the Geneva nomenclature their names are formed by adding the syllable "ol" to that of the parent hydrocarbon, followed by the word "acid"; for example, $HO.CH_2.COOH$ is *hydroxy-acetic acid* or *ethanol-acid.* They may also be considered to be oxidation products of the polyhydric alcohols, as expressed in the above case by the term *glycollic acid.*

Among the hydroxy-acids we have the same possibilities of isomerism as in the case of the chloro- and amino-acids. Similarly, the position of the substituent with regard to the carboxyl group is represented by the use of letters, *e.g.*,

$CH_3.CH_2.COOH$	$CH_3.CH(OH).COOH$	$CH_2(OH).CH_2.COOH$
Propionic acid	α-Hydroxy-propionic acid	β-Hydroxy-propionic acid.

Properties.—The hydroxy-acids possess the characteristics of both alcohols and acids. Thus the presence of the carboxyl group leads to the formation of salts, esters and amides; and the hydrogen of the alcoholic hydroxyl group is also replaceable by alkali metals and alkyl or acyl radicals.

$\begin{matrix}COOH\\\vert\\CH_2.OH\end{matrix}$	$\begin{matrix}COOC_2H_5\\\vert\\CH_2.OH\end{matrix}$	$\begin{matrix}COOH\\\vert\\CH_2.OC_2H_5\end{matrix}$
Glycollic acid	Ethyl glycollate (hydrolysable)	Ethoxyacetic acid (not hydrolysable).

[1] *Z. physiol. Ch.*, 1905, **46**, 52. [2] Abderhalden, *Z. physiol. Ch.*, 1906, **47**, 159.

The strength of the fatty acids is increased by the entrance of the hydroxyl group into the molecule, the effect being the greater the closer the hydroxyl stands to the carboxyl group. This is shown by a comparison of the dissociation constants of the acids.

The influence exerted by the position of the hydroxyl group is also clearly illustrated in the different manner in which water is eliminated from α-, β- and γ-hydroxy-acids.

α-Hydroxy-acids, on being heated, lose water in such a way that two molecules of the acid interact, the hydroxyl group of each uniting with the carboxyl group of the other molecule to form cyclic double esters known as *lactides*.

$$\begin{array}{l} \mathrm{COOH} \\ | \\ \mathrm{CH_3.CH.OH} \end{array} + \begin{array}{l} \mathrm{HO.CH.CH_3} \\ | \\ \mathrm{HOOC} \end{array} = \begin{array}{l} \mathrm{CO.O.CH.CH_3} \\ | \quad\quad | \\ \mathrm{CH_3.CH.O.CO} \end{array} + 2\mathrm{H_2O}$$

α-Hydroxy-propionic acid or lactic acid — Lactide.

β-Hydroxy-acids, when heated by themselves or with dilute sulphuric acid, generally decompose into water and unsaturated acids, the water being formed by combination of the hydroxyl group with the adjacent hydrogen atom in the α- or γ-position.

$$\underset{\beta\text{-Hydroxy-butyric acid}}{\mathrm{CH_3.CH(OH).CH_2.COOH}} = \underset{\text{Crotonic acid.}}{\mathrm{CH_3.CH:CH.COOH}} + \mathrm{H_2O}$$

The **γ- and δ-hydroxy-acids** readily eliminate water, even when in solution at the ordinary temperature, and are transformed into simple cyclic anhydrides called *lactones*.

$$\begin{array}{l} \mathrm{CH_2.CH_2.CH_2.CO} \\ | \quad\quad\quad\quad | \\ \mathrm{OH} \quad\quad\quad\quad \mathrm{HO} \end{array} = \begin{array}{l} \mathrm{CH_2.CH_2.CH_2.CO} \\ | \quad\quad\quad\quad\quad\quad | \\ \mathrm{_____O} \end{array} + \mathrm{H_2O}$$

γ-Hydroxy-butyric acid — Butyrolactone.

Methods of Formation.—Hydroxy-acids may be obtained by the following methods :—

1. From halogen-substituted fatty acids by heating with water.

$$\mathrm{CH_2Cl.COOH + HOH = CH_2OH.COOH + HCl}$$

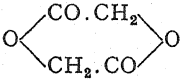
2. By the careful oxidation of polyhydric alcohols.
3. By the reduction of aldehydic or ketonic acids.
4. From amino-acids by interaction with nitrous acid (*cf.* p. 143).
5. By the addition of hydrogen cyanide to aldehydes or ketones and hydrolysis of the cyanhydrins so formed :

$$\underset{\text{Acetaldehyde}}{\mathrm{CH_3.CHO}} \xrightarrow{+\mathrm{HCN}} \underset{\text{Acetaldehyde cyanhydrin}}{\mathrm{CH_3.C(H)(OH)(CN)}} \xrightarrow{+2\mathrm{H_2O}} \underset{\text{Lactic acid.}}{\mathrm{CH_3.C(H)(OH)(COOH)}}$$

6. From fatty acids containing the tertiary $\rangle$CH group, by direct oxidation with permanganate.

$$\underset{\text{Isobutyric acid}}{\mathrm{(CH_3)_2CH.COOH}} + \mathrm{O} = \underset{\text{α-Hydroxy-isobutyric acid.}}{\mathrm{(CH_3)_2COH.COOH}}$$

The best known and most important of the hydroxy-acids are glycollic acid and ordinary or fermentation lactic acid.

Glycollic acid, *hydroxy-acetic acid,* $CH_2OH.COOH$, may be prepared by heating chloroacetic acid with water. It occurs in the green leaves of the wild vine and in unripe grapes. The acid forms crystals of m.p. 80°, which are readily soluble in water. When distilled *in vacuo*, water is given off and glycollide,  , produced.

Lactic Acids, $C_3H_6O_3$

Lactic acids are monohydroxy derivatives of propionic acid, $CH_3.CH_2.COOH$. It will be seen at once that two structural isomerides are possible, according as the hydroxy group occupies the α- or β-position. Of these, α-hydroxy-propionic acid or ordinary lactic acid, which exists in optically active modifications, is of special interest from the theoretical as well as the practical standpoint. The researches on the lactic acids, published in 1873 by Wislicenus, led him to the conclusion that differences between isomeric compounds having the same structural formula could only be accounted for by a different position of their atoms in space, a view similar to that advanced some time previously by Pasteur from his investigation into the tartaric acids. These two pieces of work formed the foundation of the theory of stereoisomerism put forward shortly afterwards by Le Bel and van't Hoff independently.

Fermentation lactic acid, *ethylidene lactic acid, racemic α-hydroxy-propionic acid,* may be obtained synthetically according to the general methods described above.

A method of practical importance consists in the "lactic fermentation" of certain substances of the sugar group, such as glucose and lactose, by means of the lactic acid bacillus. The formation of lactic acid in sour milk is a consequence of this process.

Buchner and Meisenheimer have shown that this action, like that of alcoholic fermentation, is caused by an enzyme produced in the living micro-organism, which can be separated from the living cells without losing its activity.[1]

Lactic acid is also formed from glucose, cane sugar and the pentoses by heating with caustic alkalis.

Preparation of r-*Lactic Acid.*—A dilute solution of glucose is fermented by the addition of sour milk or ripe cheese, both of which are rich in lactic acid bacilli, the temperature meanwhile being maintained at 45° to 55°. By keeping within these limits the danger of alcoholic or butyric fermentation is avoided. As the lactic bacillus is very sensitive towards free acid, the fermentation tends to come to a stand-still after a short time. In order to prevent this, the lactic acid is neutralised by adding, at the beginning of the operation, milk of lime or a suspension of chalk or zinc carbonate. By this means lactic acid is obtained in the form of its sparingly soluble calcium or zinc salt. The calcium salt is then treated with dilute sulphuric acid, or the zinc compound with hydrogen sulphide, after which water is evaporated off and the free lactic acid obtained by distillation *in vacuo*. For technical purposes the filtrate from the calcium sulphate

[1] E. Buchner and J. Meisenheimer, *Ann.*, 1906, **349**, 125.

is evaporated till the lactic acid content is about 50 per cent., and the syrupy liquid so formed is placed directly on the market.

Lactic acid is used with potassium dichromate in the dyeing industry for mordanting wool, where it is of special service on account of its high solubility and lack of corrosive action. It is used by tanners for removing lime from pelts, and is also employed for medicinal and domestic purposes.

As may be seen from its formula, α-hydroxy-propionic acid contains an *asymmetric carbon atom*. According to theory it should therefore exist in three stereoisomeric forms, viz., a dextro- and a lævo-rotatory modification, and a racemic inactive compound composed of equal amounts of these two (see p. 32). All three forms are known. The acid described above as produced by synthesis or fermentation is the racemic form, being optically inactive and capable of separation into its active components by any of the usual methods (p. 38). It forms deliquescent crystals of melting-point 18°, and is readily soluble in water, alcohol and ether. The zinc salt is only sparingly soluble in water, from which it separates with 3 mols. of water of crystallisation.

Sarco-lactic acid, d-*lactic acid*, or *para-lactic acid* is the dextro modification of α-hydroxy-propionic acid. It occurs in meat juice and is most conveniently prepared from Liebig's extract of meat. It is also formed from racemic lactic acid by exposing it to the action of *Penicillium glaucum*, whereby the *l*-form is destroyed.

d-Lactic acid is the first recognisable degradation product of glucose, the presence of which can be traced in the body; under favourable conditions of concentration in the liver it may be reconverted into glucose. In the muscles it appears to be formed from carbohydrate-phosphoric acid compounds,[1] one of which has been isolated from fresh muscle.

l-*Lactic acid* may be obtained from the *r*-acid by resolution with strychnine, and is also formed by the action of *Bacillus acidi laevolactici* on a solution of cane sugar.

Active lactic acids differ from the racemic compound in forming a readily soluble zinc salt, crystallising with 2 mols. H_2O.

Ethylene lactic acid, *β-hydroxy-propionic acid, hydracrylic acid,* $CH_2OH.CH_2.COOH$, is obtained from β-chloro- or β-iodo-propionic acid by warming with water and silver oxide, or from ethylene cyanhydrin, $CH_2OH.CH_2CN$, by hydrolysis. It is a syrupy liquid which is readily transformed into acrylic acid, $CH_2:CH.COOH$, by loss of water.

l-**β-Hydroxybutyric acid,** $CH_3.CHOH.CH_2.COOH$, results in the animal organism from the degradation of fats and many amino-acids (*e.g. d*-amino-valeric acid, leucine). It is eliminated in large quantities in the urine in severe cases of diabetes, and its presence in the blood is characteristic of the final stages of the disease (see also p. 193). The acid forms hygroscopic crystals, m.p. 49° to 50°, and volatilises in steam, whereby it is decomposed to give water and α-crotonic acid.

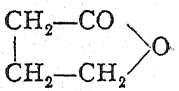
Aleuritic acid, trihydroxy-palmitic acid, $CH_2OH.(CH_2)_5.CHOH.CHOH.(CH_2)_7.COOH$, has been isolated as a hydrolysis product of shellac.[2]

[1] G. Embden and Laquer, *Z. für physiol. Chem.*, 1917, **98**, 181; G. Embden and Zimmermann, *ibid.*, 1927, **167**, 114. [2] W. Nagel, *Ber.*, 1927, **60**, 605.

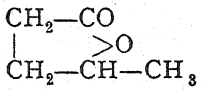
Lactones

Nomenclature.—As already stated on p. 234, the inner anhydrides of hydroxy-acids, formed by splitting off a molecule of water between the carboxyl and the hydroxyl groups, are known as lactones. These anhydrides are formed particularly easily by γ- and δ-hydroxy-acids, which yield γ- and δ-lactones respectively. A few α-, β- and ε-lactones are also known.

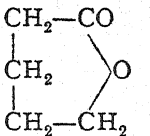
According to the Geneva nomenclature, the names of the lactones terminate in "olide," *e.g.* γ-valerolactone or 1 : 4-pentanolide. The various compounds are distinguished by use of Greek letters or numbers representing the relative positions of the carboxyl and hydroxyl groups.



Butyrolactone
(Butanolide)



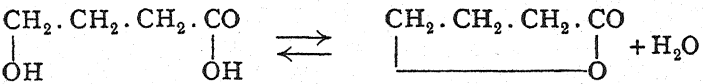
γ-Valerolactone
(1 : 4-pentanolide)



δ-Valerolactone
(1 : 5-pentanolide).

Formation.—Reactions leading to the formation of lactones depend in most cases on the elimination of water from hydroxy acids, or of hydrogen halide from halogen-substituted acids, in which the hydroxyl or halogen occupies the position corresponding to the particular lactone required.

1. The majority of γ-hydroxy-acids part with water immediately at the ordinary temperature, even in aqueous solution, and cannot therefore be isolated as such. But lactone formation resembles esterification in being a reversible reaction; consequently the change is never complete in the presence of water, a state of equilibrium being set up between the acid on the one hand and the lactone and water on the other. The

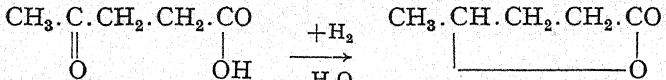


γ-Hydroxy-butyric acid — Butyrolactone.

introduction of substituent alkyl groups decidedly favours the formation of lactones.

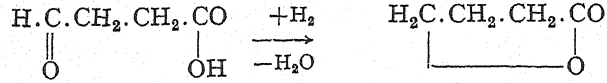
In order to convert the hydroxy-acid into the lactone as rapidly and as completely as possible, the solution is boiled with a small quantity of hydrochloric or sulphuric acid, which brings about a marked acceleration of the change.

2. Ketonic acids containing the keto group in the γ- or δ-position may be converted into lactones by means of nascent hydrogen, a more or less unstable hydroxy-acid being first formed. As the keto-acids are easily prepared, this method is of practical importance. The reduction is usually carried out in alkaline solution using sodium amalgam.



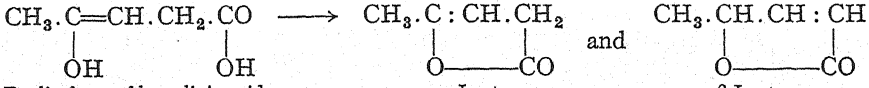
Laevulinic acid — γ-Valerolactone.

γ-Aldehydic acids may also be reduced to lactones, *e.g.*



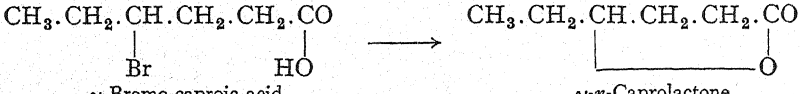
Aldehydo-propionic acid — Butyrolactone.

Many γ-ketonic acids are directly converted into lactones by distillation, or treatment with dehydrating agents. Under these conditions two structurally isomeric unsaturated lactones are usually formed which differ from one another in the position of the double bond in the lactone ring. An example of this type is the formation of two *lactones of angelic acid* by the distillation of laevulinic acid :



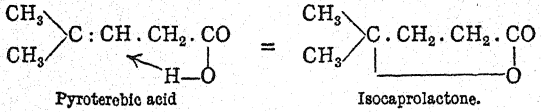
Enolic form of laevulinic acid (Hydroxy-angelic acid) — α-Lactone — β-Lactone.

3. γ-Halogen-substituted acids are also as a rule very unstable, and on formation they frequently undergo immediate transition into the lactone. The reactive bromo-acids are generally utilised in this method of preparation, *valerolactone*, for example, being formed from γ-bromo-valeric acid, and *caprolactone* from γ-bromo-caproic acid.



γ-Bromo-caproic acid — γ-*n*-Caprolactone.

4. Lactones may also be obtained from the unsaturated acids. In a few instances a direct rearrangement of an unsaturated acid into an isomeric β-lactone has been observed, a reaction which may be considered as the addition of the carboxyl group to the double bond, *e.g.*,



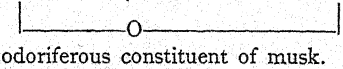
Pyroterebic acid — Isocaprolactone.

Under the influence of fuming hydrobromic acid many βγ- and γδ- unsaturated acids are converted into lactones, the unstable saturated bromo-acids first formed very readily parting with hydrogen bromide.

Unsaturated acids are more conveniently converted into lactones by warming them for a few minutes with equal volumes of sulphuric acid and water.

This reaction is in every way analogous to the formation of alcohols from unsaturated hydrocarbons under the influence of aqueous sulphuric acid. In addition to these simple methods of formation, lactones may be obtained by various synthetic processes to be described later.

Certain lactones, such as *coumarin* and the *coumarins* (p. 459), are found free in nature. An interesting example is **ambrettolide,**[1]



a lactone with a 17-membered ring which is the odoriferous constituent of musk. It has been isolated from musk-seed oil as a colourless viscous oil, b.p. 187° to 190° under 16 mm. pressure.

[1] M. Kerschbaum, *Ber.*, 1927, **60**, 902. Compare also the investigations of Ruzicka into the constitution of civetone, *Helv. Chim. Acta*, 1926, **9**, 230, 249.

Chemical Properties.—Owing to the stability of the lactone ring, lactones have in general little tendency to enter into chemical reaction, which is not unexpected considering their nature as inner esters.

Just as water converts lactones into hydroxy-acids, treatment with hydrogen chloride, bromide or iodide converts them into halogenated acids. In this way γ-chloro-, bromo- and iodobutyric acids are readily obtained from butyrolactone.

$$\begin{array}{l} CH_2 . CH_2 . CH_2 \\ | \qquad\qquad | \\ O\text{———}CO \end{array} + HX = XCH_2 . CH_2 . CH_2 . COOH$$

Although lactones are not attacked in the cold by alkali carbonates, they are hydrolysed like all esters by free alkalis, with the formation of salts of the corresponding hydroxy- or keto-acids.

Lactones also unite with ammonia, yielding amides of hydroxy-acids

$$\begin{array}{l} CH_2 . CH . CH_3 \\ | \quad \diagdown O \\ CH_2 . CO \end{array} + NH_3 = \begin{array}{l} CH_2 . CHOH . CH_3 \\ | \\ CH_2 . CO . NH_2 \end{array}$$

and with hydrazine hydrate and phenyl hydrazine to form hydrazides.

By the use of sodium amalgam in weakly acid solution, lactones of poly-hydroxy acids may be reduced to the corresponding aldoses, a reaction which is of great value in the synthesis of sugars.

5. Hydroxy-Amino-Acids

The hydroxy-amino-acids, like α-amino- and diamino-acids, are of importance in the chemistry of the proteins. One of the simplest and best known examples of this type is *serine*, $CH_2OH . CHNH_2 . COOH$, obtained as a hydrolysis product of sericin or silk gum.

Hydroxy-amino-acids are prepared by the following methods.

1. By the interaction of halogen-substituted hydroxy-acids with ammonia.

$$\underset{\text{α-Hydroxy-β-chloro-propionic acid}}{CH_2Cl—CHOH—COOH} \longrightarrow \underset{\text{α-Hydroxy-β-amino-propionic acid.}}{CH_2NH_2—CHOH—COOH}$$

2. By the action of ammonia on epihydrinic acids.

$$\underset{\text{Glycidic or epihydrinic acid}}{\begin{array}{l} O \\ \diagup\diagdown \\ CH_2—CH—COOH \end{array}} \longrightarrow CH_2NH_2—CHOH—COOH$$

3. By the combined action of hydrogen cyanide and ammonia on hydroxy-aldehydes,[1] *e.g.*,

$$\underset{\text{Glycollaldehyde-ammonia}}{CH_2OH—CH(OH)(NH_2)} \longrightarrow CH_2OH—CHNH_2—CN \longrightarrow$$

$$\underset{\substack{\text{α-Amino-β-hydroxy-propionic acid} \\ \text{(Serine).}}}{CH_2OH—CHNH_2—COOH}$$

[1] E. Fischer and Leuchs, *Ber.*, 1902, **35**, 3787.

The conversion of aldol by this method into the corresponding α-amino-γ-hydroxy-valeric acid, $CH_3.CHOH.CH_2.CHNH_2.COOH$, takes place more readily than the above reaction.[1]

4. By addition of hydrogen cyanide to amino-aldehydes and hydrolysis of the nitriles so formed.

$$CH_2OH—(CHOH)_3—CHNH_2—CHO \longrightarrow CH_2OH—(CHOH)_3—CHNH_2—CHOH—COOH$$

5. By the partial elimination of nitrogen from diamino-acids.[2]

$$CH_2NH_2—CHNH_2—COOH \longrightarrow CH_2NH_2—CHOH—COOH$$

αβ-Diamino-propionic acid.

6. By the condensation of aldehydes with glycocoll. This method, however, is only capable of limited application.[3]

7. Sörensen has developed a method of synthesising hydroxy-amino-acids which is closely related to his synthesis of diamino-acids. Thus from γ-bromo-propyl-phthalimido-malonic ester he was able to prepare α-amino-δ-hydroxy-valeric acid.

$$CH_2OH.CH_2.CH_2.CH(NH_2)COOH$$

Serine, *α-amino-β-hydroxy-propionic acid,* $CH_2OH.CHNH_2.COOH$ was discovered in 1865 by Cramer among the hydrolysis products of sericin or silk gum, and is of special interest from the chemical as well as the physiological standpoint as being the simplest and first known hydroxy-amino-acid of the aliphatic series. It was first synthesised by E. Fischer and Leuchs by method 3 above. A second synthesis, which permits of the preparation of serine from readily available starting materials, was effected by Erlenmeyer, jun. It consists in the condensation

$$HCO_2C_2H_5 + CH_2NH.COC_6H_5.CO_2C_2H_5 \xrightarrow{-EtOH} \text{I. } CHO.CHNH.COC_6H_5.CO_2C_2H_5 \xrightarrow{H_2}$$

$$\text{II. } CH_2OH.CHNH.COC_6H_5.CO_2C_2H_5 \xrightarrow{H_2SO_4} CH_2OH.CHNH_2.COOH + C_2H_5OH + C_6H_5COOH$$

of formic ester with hippuric ester, to give *formyl-hippuric ester* I. This product is then reduced to *benzoyl-serine ester* II, which on hydrolysis with very dilute sulphuric acid yields serine, benzoic acid and alcohol.

Serine separates from aqueous solution in slender leaflets, which on rapid heating melt in the neighbourhood of 240° with evolution of gas. The acid obtained by the hydrolysis of proteins is usually completely inactive, probably owing to racemisation under the influence of the reagents employed. Resolution of the racemic form may be effected by converting it first into the *p*-nitrobenzoyl compound, and resolving this

[1] E. Fischer, *Ber.*, 1906, **39**, 537. [2] Neuberg and Silbermann, *Ber.*, 1904, **37**, 341.
[3] Erlenmeyer, jun., *Ann.*, 1904, **337**, 212.

by crystallisation of the quinine or brucine salts. The subsequent removal of the *p*-nitrobenzoyl group offers no difficulty. *l*-Serine is the natural product as found in proteins, and has been isolated from silk. On reduction with hydriodic acid and phosphorus, serine is converted into alanine.

Isoserine, *α-hydroxy-β-amino-propionic acid,* $CH_2NH_2.CHOH.COOH$, is most conveniently prepared from β-chloro-lactic acid by heating with ammonia. It passes on reduction with HI and phosphorus into β-amino-propionic acid.

Cysteine III and **cystine** IV are two acids standing in close relationship to serine. Cysteine is a thio-serine and cystine the corresponding

III. CH_2SH / $CHNH_2$ / $COOH$

IV. $CH_2—S—S—CH_2$ / $CHNH_2$ $CHNH_2$ / $COOH$ $COOH$

disulphide. Both were first obtained in small amount by the hydrolysis of keratin (horn). Erlenmeyer, jun.,[1] prepared cysteine synthetically from benzoyl-serine ester by heating it with P_2S_5 and decomposing the product with concentrated hydrochloric acid. On oxidation with air it is transformed into *r*-cystine. The natural active cystine is formed from *l*-serine ester by treatment with PCl_5, which converts it into β-chloro-α-amino-propionic ester, and warming the free acid from the latter for 1½ hours to 100° with aqueous barium hydrosulphide. Under these conditions the halogen is exchanged for —SH, yielding active cysteine, which after removal of excess hydrosulphide and addition of ammonia may be oxidised by air to active cystine.[2]

The constitution of cysteine was originally confirmed by its conversion into taurine (see p. 248). This relationship is also of significance in the living organism, since cysteine is the parent substance of taurine, which forms one component of an important bile acid, *taurocholic acid*, found in ox-gall. Cysteine is transformed into taurine by decarboxylation followed by oxidation: $HS.CH_2.CH(NH_2).COOH \longrightarrow HO_3S.CH_2.CH_2.NH_2$. *The reversible dehydrogenation of cysteine to cystine plays a fundamental part in the oxidative processes which occur in living tissues* [3] (*cf.* p. 231).

Cysteine, cystine and a third amino-acid, **methionine**, are the only known sulphur compounds entering into protein structure. Methionine has been synthesised by Barger [4] and shown to be *γ-methylthiol-α-amino-butyric acid,* $CH_3S.CH_2.CH_2.CH(NH_2).COOH$.

[1] *Ann.*, 1904, **337**, 241. [2] E. Fischer and Raske, *Ber.*, 1908, **41**, 893. For the preparation of cystine from wool see A. R. T. Merrill, *J. Am. C. S.*, 1921, **43**, 2688. [3] F. G. Hopkins, *Skand. Arch. f. Physiologie*, 1926, **49**, 33. [4] Barger and Coyne, *Biochem. J.*, 1928, **22**, 1417. Barger and Weichselbaum, *Biochem. J.*, 1931, **25**, 997. The acid was first isolated by J. Mueller (*J. Biol. Chem.*, 1923, **56**, 157).

XII

Polyhydric Alcohols

In addition to the monohydric alcohols already described (p. 145), polyhydric alcohols are known containing two or more hydroxyl groups in the molecule. Only in rare cases are more than one of these groups found attached to the same carbon atom. Polyhydric alcohols usually undergo all the reactions quoted under monohydric alcohols, although, as would be expected, the changes suffered by virtue of the single hydroxyl grouping may be repeated several times in the case of the polyhydric compounds. Derivatives may thus be formed which, like hydroxy-acids and amino-alcohols, contain more than one typical class-group in the molecule. These compounds generally possess the characteristics of both of the classes they represent.

I.—DIHYDRIC ALCOHOLS OR GLYCOLS, AND THEIR DERIVATIVES

Dihydric alcohols take their name from glycol, the simplest member of the series, and may be derived from hydrocarbons by replacing two hydrogen atoms, attached to different carbon atoms, by hydroxyl groups. They are distinguished as α-, β-, γ- or δ-glycols, according as the hydroxyl groups stand in the 1 : 2, 1 : 3, 1 : 4, or 1 : 5 positions to one another.

Methods of Formation.—Dihydric alcohols may be obtained in the same manner as the mono-substituted compounds from the corresponding halogen derivatives, by heating them with water or potassium carbonate, or by bringing them into reaction with silver or potassium acetate and hydrolysing the diacetates so formed. This reaction is of special importance for the preparation of α-glycols, since the corresponding 1 : 2-dibromides are readily obtained by the addition of bromine to olefins. In this way glycol was first prepared by Würtz.

$$CH_2:CH_2 \xrightarrow{+Br_2} CH_2Br.CH_2Br \xrightarrow{+2H_2O} CH_2OH.CH_2OH + 2HBr$$

Other glycols may be obtained in a similar manner. For example, allyl bromide combines with hydrobromic acid to form trimethylene bromide, which may readily be converted into trimethylene glycol.

$$\underset{\text{Trimethylene bromide}}{CH_2Br.CH_2.CH_2Br} \xrightarrow{2H_2O} \underset{\text{Trimethylene glycol.}}{CH_2OH.CH_2.CH_2OH}$$

It has already been mentioned on p. 121 that α-glycols are formed by the cautious oxidation of olefins with aqueous potassium permanganate. They are also produced, together with secondary alcohols, when ketones are reduced electrolytically or by means of sodium. Under these conditions acetone yields isopropyl alcohol and **pinacol** (tetramethyl-ethylene glycol, formerly known as *pinacone*). The latter on treatment with

dilute sulphuric or hydrochloric acid undergoes a remarkable intramolecular rearrangement with elimination of water to form **pinacolone** (originally *pinacoline*).

$$\underset{\text{Acetone}}{(CH_3)_2CO} \xrightarrow{2H} \underset{\text{Pinacol}}{(CH_3)_2C(OH)\cdot C(OH)(CH_3)_2} \xrightarrow{-H_2O} \underset{\text{Pinacolone.}}{(CH_3)_3C\cdot CO\cdot CH_3}$$

In a similar manner, by the reduction of various ketones, a number of **tetra-alkylated ethyleneglycols** have been prepared, which are classed as **pinacols** and show the same behaviour with dilute mineral acids as pinacol itself.

More recently glycols have been obtained by the action of alkyl magnesium halides on diketones, keto-alcohols, aldehydo-alcohols and dicarboxylic esters. Zelinsky, for example, obtained pinacol from diacetyl and methyl magnesium iodide.

$$\underset{\text{Diacetyl.}}{CH_3CO.COCH_3} \xrightarrow{2CH_3.MgI} \underset{\text{Pinacol.}}{(CH_3)_2C(OH).C(OH)(CH_3)_2}$$

Properties.—Glycols are generally viscous, colourless and sweet-tasting liquids (hence the name), which are easily soluble in water and alcohol but difficultly soluble in ether. Their boiling-points lie considerably higher than those of the monohydric alcohols with a similar carbon chain.

The chemical behaviour of the glycols may be deduced from that of the simple alcohols. Thus the hydroxyl group may be displaced by halogen, or its hydrogen atom replaced by an alkyl or acyl group, or by an alkali metal. Primary glycols also undergo oxidation to aldehyde and acid. Since, however, we are dealing with compounds containing two hydroxyl groups in the molecule, it is obvious that all these reactions may take place in two stages, as indicated in the following formulæ.

$$\underset{\text{Monosodium derivative}}{\begin{matrix}CH_2\cdot ONa\\ |\\ CH_2\cdot OH\end{matrix}} \quad \underset{\text{Disodium derivative}}{\begin{matrix}CH_2\cdot ONa\\ |\\ CH_2\cdot ONa\end{matrix}}; \quad \underset{\text{Glycol monoethyl ether}}{\begin{matrix}CH_2\cdot OC_2H_5\\ |\\ CH_2\cdot OH\end{matrix}} \quad \underset{\text{Glycol diethyl ether.}}{\begin{matrix}CH_2\cdot OC_2H_5\\ |\\ CH_2\cdot OC_2H_5\end{matrix}};$$

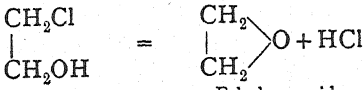
$$\underset{\text{Glycol monoacetate}}{\begin{matrix}CH_2\cdot O\cdot COCH_3\\ |\\ CH_2\cdot OH\end{matrix}} \quad \underset{\text{Glycol diacetate.}}{\begin{matrix}CH_2\cdot O\cdot COCH_3\\ |\\ CH_2\cdot O\cdot COCH_3\end{matrix}};$$

$$\underset{\text{Glycollic aldehyde}}{\begin{matrix}CH:O\\ |\\ CH_2\cdot OH\end{matrix}} \quad \underset{\text{Glyoxal}}{\begin{matrix}CH:O\\ |\\ CH:O\end{matrix}}; \quad \underset{\text{Glycollic acid}}{\begin{matrix}COOH\\ |\\ CH_2\cdot OH\end{matrix}} \quad \underset{\text{Glyoxalic acid}}{\begin{matrix}COOH\\ |\\ CH:O\end{matrix}} \quad \underset{\text{Oxalic acid.}}{\begin{matrix}COOH\\ |\\ COOH\end{matrix}}$$

By the action of phosphorus pentachloride both hydroxyl groups are replaced by chlorine, giving the neutral hydrochloric acid esters of the glycols, *e.g.* $CH_2Cl.CH_2Cl$, which may also be considered as dichloro-substitution products of the paraffins. On the other hand, when heated with hydrogen chloride or bromide only one hydroxyl group is replaced by halogen, with the production of **chlorohydrins** and **bromohydrins :**

$$\begin{matrix}CH_2\cdot OH\\ |\\ CH_2\cdot OH\end{matrix} + HCl = \underset{\text{Ethylene chlorohydrin.}}{\begin{matrix}CH_2\cdot Cl\\ |\\ CH_2\cdot OH\end{matrix}} + H_2O$$

It is an easy matter to replace the halogen in these halogenohydrins by other groups such as NH_2 or SO_3H, and they are therefore utilised in preparing the majority of glycol derivatives. When heated with solid sodium hydroxide the chlorohydrins split off hydrochloric acid to form **alkylene oxides,** which are inner anhydrides of the glycols.



Ethylene oxide.

By means of dehydrating agents, such as P_2O_5 and zinc chloride, the β-, γ- and δ-glycols are also directly transformed into cyclic oxides of the same type.

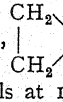
Ethylene glycol, *glycol, ethan-diol,* $CH_2OH.CH_2OH$, may be formed according to the methods already described. Technically, it is used in large quantities for mixing with water to prevent freezing (*anti-freeze*), *e.g.* in radiators of motor cars and also as the cooling liquid in aeroplane engines. For this purpose it is prepared from the ethylene obtained as a by-product in " cracking " processes, by reaction with aqueous hypochlorous acid to give glycol chlorohydrin, followed by hydrolysis with dilute alkali. Glycol is an oily, colourless liquid, b.p. 197·5° and sp. gr.

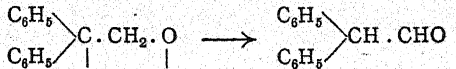
$$CH_2 : CH_2 \rightarrow CH_2OH.CH_2Cl \rightarrow CH_2OH.CH_2OH$$

1·125, which is miscible with water and alcohol but only dissolves sparingly in ether. On oxidation it yields glycollic acid and finally oxalic acid. Certain ethers and organic esters of glycol, especially *glycol mono-ethyl ether* and *glycol diacetate*, are employed as solvents for cellulose esters.

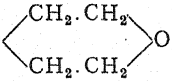
Among the derivatives of dihydric alcohols the most important of the halogen and amino compounds are described below. Oxidation products are dealt with later in another section.

Glycol chlorohydrin, *ethylene chlorohydrin,* $CH_2Cl.CH_2OH$, b.p. 130°, formed by leading hydrogen chloride into hot glycol, or ethylene into aqueous hypochlorous acid, is a liquid which is miscible in all proportions with water. When treated with potassium cyanide it is converted into ethylene cyanhydrin, $CH_2CN.CH_2OH$, the nitrile of ethylene-lactic acid.

Ethylene oxide,  , is formed by distilling the chlorohydrin with solid sodium hydroxide. It boils at 13°, possesses an ethereal smell and has a marked tendency to unite with a variety of substances, combination being accompanied by the rupture of the ring; consequently it is frequently employed as a starting material for the preparation of other compounds. For example, in the presence of water it combines with ammonia and amines to form hydroxy-ethylamine bases (see below). Alkylene oxides and their substitution products may also undergo intramolecular rearrangement to yield aldehydes, *e.g.*,



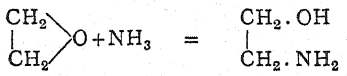
Diphenyl-ethylene oxide — Diphenyl-acetaldehyde.

Dioxan,  , is used as a solvent, *e.g.* for cellulose acetate. It melts at 9°, boils at 102° and is miscible in all proportions with water. One method of preparation is to heat glycol with concentrated sulphuric acid.

Amines derived from Dihydric Alcohols

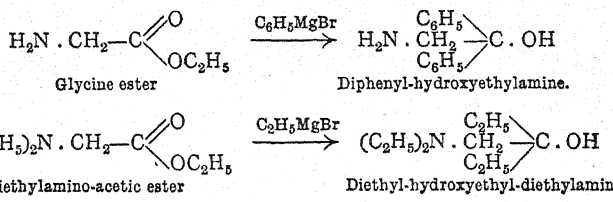
(*a*) Monoamines, Hydroxy-alkyl Bases

Hydroxy-ethylamine, *aminoethyl alcohol,* $CH_2OH.CH_2NH_2$, is the nitrogenous base of many phosphatides, *e.g.* of the kephalins (see p. 202). It is produced during the putrefaction of serine in the absence of air (under a thick layer of paraffin),[1] but is best obtained by the combination of ethylene oxide with ammonia in aqueous solution. It is a viscous, strongly basic liquid, b.p. 171°.

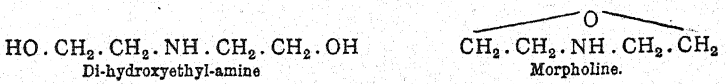


In a similar manner **di-hydroxyethyl-amine,** $(HO.CH_2.CH_2)_2NH$, and **tri-hydroxy-ethyl-amine,** $(HO.CH_2.CH_2)_3N$, may be prepared. When primary and secondary amines are employed instead of ammonia, the reaction with ethylene oxide leads to the formation of hydroxyethyl-alkylamines,[2] $HO.CH_2.CH_2.NHR$ and $HO.CH_2.CH_2.NR_2$. Dimethylamine, for example, reacts with ethylene oxide to form **hydroxyethyl-dimethyl-amine,** $HO.CH_2.CH_2.N(CH_3)_2$, which is of interest as being one of the fission products of the alkaloid morphine (see index).

Hydroxyalkyl-amines may also be obtained by the application of the Grignard reaction to amino-esters,[3] *e.g.*,



The above-mentioned di-hydroxyethyl-amine is closely related to **morpholine,** a compound which was formerly of interest in connection with the constitution of morphine. Morpholine is the inner ether of di-hydroxyethyl-amine,



and may be prepared by heating the latter to 160° with 70 per cent. sulphuric acid, in the same way as the δ-glycols may be converted into their anhydrides. It is a strongly basic liquid, b.p. 128°. As will be seen later, the idea that the alkaloid morphine is derived from this substance has been abandoned.

From aminoethyl alcohol it is possible to prepare **aminoethyl ether,** $NH_2.CH_2.CH_2.OC_2H_5$. This is one of the simplest of the ether-bases, and may be obtained by heating aminoethyl alcohol at 150° to 160° with concentrated hydrochloric acid, when

[1] F. F. Nord, *Biochem. Zeitsch.*, 1919, **95**, 281. [2] The hydroxy-alkyl bases are sometimes known under the name of *hydramines*, and the hydroxy-dialkyl bases as *alkamines*. [3] Paal and Weidenkaff, *Ber.*, 1906, **39**, 810; *cf.* also *C.*, 1906, **I**, 1584, 1586.

it is converted into β-chloro-ethylamine hydrochloride; this on being further treated at 150° to 160° with a solution of sodium ethylate yields the amino-ether.

$$\underset{\text{Aminoethyl alcohol}}{H_2N.CH_2.CH_2.OH} \xrightarrow{HCl} \underset{\beta\text{-Chloro-ethylamine.}}{H_2N.CH_2.CH_2Cl}$$

$$\xrightarrow{NaOC_2H_5} \underset{\text{Aminoethyl ether.}}{H_2N.CH_2.CH_2.OC_2H_5}$$

Aminoethyl ether is a very mobile liquid with a strong smell and an alkaline reaction. It mixes with water, alcohol and ether in all proportions, and the majority of its salts are readily soluble in water.

Dimethylaminoethyl ether, $(CH_3)_2N.CH_2.CH_2.OC_2H_5$, was isolated by Knorr as a disruption product of the alkaloids morphine, codeine and thebaine. It is formed by the interaction of dimethylamine and iodo-ether,

$$(H_3C)_2NH + I.CH_2.CH_2.O.C_2H_5 \longrightarrow \begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>\!N.CH_2.CH_2.O.C_2H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad H\ \ I$$

or from chloroethyl-dimethylamine and sodium ethoxide,

$$\begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>\!N.CH_2.CH_2.Cl + NaOC_2H_5 = \begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>\!N.CH_2.CH_2.OC_2H_5 + NaCl$$

The base boils at 120° to 121° under 750 mm. pressure.

Closely related to hydroxyethylamine is *choline*, which is of importance physiologically.

Choline, *hydroxyethyl-trimethyl-ammonium hydroxide*, *bilineurine*, $HO.CH_2.CH_2.N(CH_3)_3.OH$, is very widely distributed in plant and animal organisms, and is probably a constant product of plant life which is necessary for the building up of all plant cells. The name choline was suggested by Strecker, who discovered the substance in the bile of cattle and swine.

Choline occurs as a constituent of lecithin in the brain and in egg yolk (see p. 201). It has been obtained as a disruption product of the alkaloid sinapine on treatment with baryta, and may also be prepared from seeds.

The constitution of choline is shown by its hydrolytic products—a concentrated aqueous solution of the substance decomposes on boiling into trimethylamine and glycol—and also by its manner of formation. It may be obtained synthetically by heating trimethylamine with ethylene chlorohydrin, or by allowing trimethylamine and ethylene oxide to react in aqueous solution at ordinary temperature.

$$\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>\!O + N(CH_3)_3 + H_2O = (CH_3)_3N\!<\!\begin{matrix} CH_2.CH_2.OH \\ OH \end{matrix}$$

Choline is a non-crystallisable syrupy liquid, deliquescent in air and miscible in all proportions with water. It has a strong alkaline reaction and little physiological activity. On oxidation it is converted into betaïne (see p. 226).

Muscarine is the poisonous principle of the fungus *Amanita muscaria*, and is closely

related to choline, although its constitution is not yet established with certainty. Possibly it is a basic hydroxy-aldehyde [1] of the formula $C_2H_5.CHOH.CH(CHO).N(CH_3)_3OH$.

N-Dimethyl-vinylamine $CH_2:CH.N(CH_3)_2$, has been obtained by the dry distillation of neurine chloride.[2] It is a mobile liquid, b.p. 37° to 38°, which with acids is decomposed rapidly into acetaldehyde and dimethylamine. It shows a great tendency to polymerise, forming a white solid mass.

Neurine, *vinyl - trimethyl - ammonium hydroxide*, $CH_2:CH.N(CH_3)_3OH$, was discovered together with choline in 1865, by heating the brain of cattle with baryta-water. It is produced during the putrefaction of choline, or on boiling the latter with baryta-water. Neurine is also found among the ptomaines formed by the putrefaction of proteins, particularly in dead bodies. Unlike choline, to which it is so closely related in constitution, neurine is a powerful poison.[3]

(*b*) Alkylene Diamines

Alkylene diamines are an interesting series of compounds which may be derived from glycols by the replacement of both hydroxyl groups by amino groups.

They may be prepared synthetically by the methods used for alkyl amines (pp. 168 *et seq.*), *e.g.* by the action of ammonia on alkylene bromides, $C_nH_{2n}Br_2$, or by the reduction of alkylene cyanides, $C_nH_{2n}(CN)_2$. Certain diamines are also formed during the putrefaction of flesh.

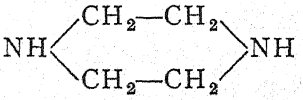
They are liquids or low melting solids of strong basic properties, which by loss of ammonia readily pass into cyclic imides.

Ethylene diamine, $NH_2CH_2.CH_2NH_2$, may be obtained together with other products by heating ethylene dibromide to 100° with alcoholic ammonia.

$$Br.CH_2.CH_2.Br+2NH_3 = NH_2.CH_2.CH_2.NH_2+2HBr$$

It melts at 8°, boils at 116°, and unites with water to form a hydrate of m.p. 10° and b.p. 118°. When the hydrochloride of ethylene diamine is heated it is converted into piperazine.

Piperazine, *diethylene diamine*, *hexahydropyrazine*,



is also produced by the reduction of pyrazine. It is a strongly basic compound, m.p. 104° and b.p. 145°, which is soluble in water. Piperazine forms a readily soluble urate and was formerly used as a remedy for rheumatism and gout.

Tetramethylene diamine, *putrescine*, 1 : 4-*diamino-butane*,

$$NH_2.CH_2.(CH_2)_2.CH_2.NH_2$$

is formed by the putrefaction of flesh and of ornithine (see p. 227). It is found together with hyoscyamine in *Hyoscyamus muticus*, and may be prepared by the reduction of ethylene cyanide,

$$NC.CH_2.CH_2.CN+8H = H_2N.CH_2.CH_2.CH_2.CH_2.NH_2$$

[1] Kögl, Duisberg and Erxleben, *Ann.*, 1931, 489, 156. [2] K. H. Meyer and H. Hopff, *Ber.*, 1921, 54, 2274. [3] For the manner in which the physiological activity of choline, neurine and allied compounds is related to their chemical constitution compare E. Schmidt, *Ann.*, 1904. 337, 37.

or better of δ-phthalimido-*n*-butyronitrile.[1] A more recent method is to shake adipic acid, dissolved in concentrated sulphuric acid, with a solution of hydrazoic acid in chloroform. Tetramethylene diamine melts at 27°,

$$\begin{matrix}CH_2.CH_2.COOH\\ |\\ CH_2.CH_2.COOH\end{matrix} + 2N_3H = \begin{matrix}CH_2.CH_2.NH_2\\ |\\ CH_2.CH_2.NH_2\end{matrix} + 2N_2 + 2CO_2$$

and when heated loses ammonia to form **pyrrolidine** or *tetrahydropyrrole*.

$$\begin{matrix}CH_2—CH_2.NH_2\\ |\\ CH_2—CH_2.NH_2\end{matrix} = \begin{matrix}H_2C—CH_2\\ |\quad\quad\rangle NH\\ H_2C—CH_2\end{matrix} + NH_3$$

Pyrrolidine.

Pentamethylene diamine, *cadaverine*, 1 : 5 - *diamino* - *pentane*, $NH_2.CH_2.(CH_2)_3.CH_2.NH_2$, is of physiological interest, as it occurs among the products formed by the putrefaction of proteins and is therefore present in the body after death. It may be obtained synthetically by the reduction of trimethylene cyanide, $CN.(CH_2)_3.CN$. A more convenient method is to treat benzoyl piperidine with phosphorus pentachloride and to replace the halogen atoms in the resulting 1 : 5-dichloropentane with amino groups, as indicated on p. 685. This process is reversed when pentamethylene diamine hydrochloride is heated, in which case ammonia is split off and **piperidine** or hexahydro-pyridine formed.

$$\begin{matrix}CH_2 & CH_2.NH_2\\ H_2C & \\ CH_2 & CH_2.NH_2\end{matrix} = \begin{matrix}CH_2 & CH_2\\ H_2C & \rangle NH\\ CH_2 & CH_2\end{matrix} + NH_3$$

Piperidine.

Taurine, *aminoethyl sulphonic acid*, $\begin{matrix}CH_2—NH_2\\ |\\ CH_2.SO_3H\end{matrix}$ or $\begin{matrix}CH_2—\overset{+}{N}H_3\\ |\\ CH_2—SO_3^-\end{matrix}$ is of interest in connection with the above amino compounds. It is found combined with cholic acid as *taurocholic acid* in ox-gall (hence the name taurine) and in the gall of many other animals. It is best prepared from the abalone, *Haliotis*, a mollusc which occurs abundantly on the Pacific coast.[2] Synthetically it may be obtained by treating chloroethyl sulphonic acid, $CH_2Cl.CH_2.SO_3H$, with ammonia. It is a crystalline compound which melts with decomposition at 240°. Nitrous acid converts it into *isethionic acid* (hydroxyethyl-sulphonic acid), $CH_2OH.CH_2.SO_3H$. In the animal organism taurine is formed from cysteine by oxidation and loss of carbon dioxide,

$$HS.CH_2.CH(NH_2).COOH \longrightarrow HO_3S.CH_2.CH_2.NH_2.$$

II.—TRIHYDRIC ALCOHOLS

These compounds contain three hydroxyl groups attached to three different carbon atoms. They may be prepared from unsaturated monohydric alcohols, either by treating with bromine and heating the resulting

[1] W. Keil, *Ber.*, 1926, **59**, 2816. [2] C. A. Schmidt and T. Watson, *J. Biol. Chem.*, 1918, **33**, 499.

dibromo-alcohols with water, or by cautious oxidation with alkaline permanganate solution. Their chemical character may be deduced from the presence of three alcoholic hydroxyl groups in the molecule, which can be brought into reaction individually or simultaneously to form ethers, esters and other derivatives (p. 243).

Glycerol or *glycerine*, $CH_2OH.CHOH.CH_2OH$, is prepared technically in large quantities by the saponification of fats during the manufacture of soap and free fatty acids (p. 199). It is most easily obtained in the pure state when the saponification is effected by means of steam. The crude glycerol is purified by steam distillation, decolorised with animal charcoal and finally concentrated under diminished pressure.

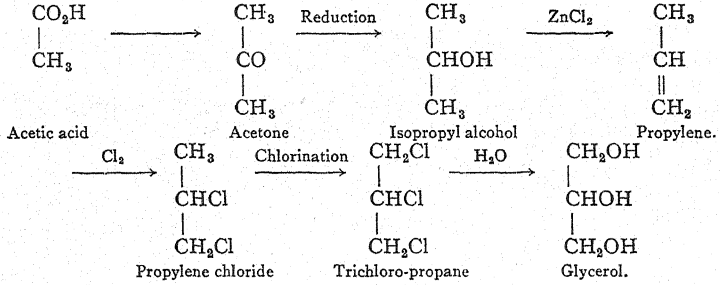
Glycerol is also prepared technically by a fermentation process.[1] Investigation showed that the proportions of the products formed during the fermentation of sugar with yeast are greatly influenced by the presence of substances of an alkaline reaction. Thus the addition of salts such as disodium phosphate, sodium acetate, ammonium carbonate and sodium or magnesium bicarbonate to a 10 per cent. solution of sugar, which is subsequently fermented with yeast at 30° to 35°, leads to the formation of considerable amounts of glycerol. Alkaline solutions of this nature, however, provide an excellent nutrient medium for the development of all kinds of bacteria, particularly lactic bacilli. These not only use up a large proportion of the sugar, but also lead to the production of impure glycerol which can only be purified with great difficulty. This defect was finally overcome by employing disodium sulphite as the alkaline salt. A concentration of 90 per cent. sulphite (calculated with respect to the sugar) is sufficient to kill off or hinder the propagation of the lactic bacilli present, and in addition the sulphite has been found to be specifically active in the formation of glycerol. With increasing proportion of sulphite the alcoholic fermentation of sugar is influenced in such a way that the production of alcohol and CO_2 diminishes, while, on the other hand, that of glycerol and acetaldehyde increases. The yield of glycerol rises from 23·1 per cent. with the addition of 40 per cent. Na_2SO_3 to 36·77 per cent. with the addition of 200 per cent. Na_2SO_3. Equally good results are obtained by the use of other sugars or of molasses, or of different types of yeast. Another advantage is that the same yeast may be used over and over again with undiminished yields, although from time to time a "recuperative" fermentation without the addition of sulphite is recommended. During the glycerol fermentation over 10 per cent. of acetaldehyde is formed as a by-product. This is due to the sulphite reacting with escaping carbon dioxide to give bicarbonate and bisulphite. The latter then combines with the aldehyde to form the bisulphite compound, which is not further attacked by yeast. With the aid of this process, which can be operated without difficulty on the large scale, Germany was able to manufacture during 1914-1918 more than 1 million kilograms

[1] Connstein and Lüdecke, *Ber.*, 1919, **52**, 1385. C. Neuberg, *Biochem. Zeitsch.*, 1916, **78**, 238; **89**, 365; **92**, 234 (1918).

of glycerol per month. The technical yield of glycerol is 20 to 25 per cent. calculated on the sugar employed.

Glycerol is also produced from sugar in the animal organism. As glycerol is an integral component of fats, this explains the manner in which carbohydrates are stored up in the body in the form of fats.

A reaction of theoretical interest is the formation of glycerol from allyl alcohol by oxidation with permanganate, $CH_2:CH.CH_2OH \longrightarrow CH_2OH.CHOH.CH_2OH$. Glycerol has also been synthesised from acetic acid, which may be built up from its elements in a variety of ways, *e.g.* acetylene+water $\longrightarrow$ aldehyde $\longrightarrow$ acetic acid. The acid was first converted into acetone, and thence through isopropyl alcohol, propylene and trichloro-propane to glycerol, as in the following scheme.



Pure glycerol is a colourless viscous syrup of sweet taste (from which is derived its name) and of sp. gr. 1·265 at 15°. It boils at 290° at the ordinary pressure and at 170° under 12 mm. At 0° it gradually solidifies to transparent crystals which melt at 17°. It is miscible in all proportions with water and alcohol, but is insoluble in ether. Glycerol forms soluble alcoholates with alkalis and other metallic hydroxides, and when heated with dehydrating agents yields acrolein, $CH_2:CH.CHO$. As has already been seen, glycerol is the starting-point in the preparation of a number of organic compounds.

On careful oxidation with bromine or nitric acid, glycerol is converted into glycerose, the main constituent of which is *dihydroxy-acetone*, $CH_2OH.CO.CH_2OH$. Under the influence of dilute alkalis the latter polymerises to a sugar *acrose*, $C_6H_{12}O_6$.

Most of the glycerol manufactured is converted into nitroglycerine, but a small proportion is utilised in the preservation of such articles of food as require to be kept moist (fruits, etc.). Other uses to which it is put include the manufacture of cosmetics and skin preparations, colour printing and the production of shoe blacking.

Since a mixture of glycerol and water does not readily freeze or evaporate, it is employed in this form in gas meters, and other instruments containing a liquid seal, which are necessarily exposed to extremes of temperature.

Nitroglycerine, *glyceryl trinitrate*, $C_3H_5(O.NO_2)_3$, is obtained by treating glycerol with a mixture of nitric and sulphuric acids.

$$C_3H_5(OH)_3+3HNO_3 = C_3H_5(ONO_2)_3+3H_2O$$

The name nitroglycerine is misleading, as the compound it describes

is no nitro-compound but an ester of nitric acid, which is hydrolysed with alkalis in the normal manner to give glycerol and a metallic nitrate.

In the *preparation of nitroglycerine* pure anhydrous glycerol is added in a thin stream, with continuous stirring, to a well-cooled mixture of nitric and sulphuric acids. The reaction proceeds best at 20° to 25°, and the temperature must not be allowed to rise above 30°. When interaction is complete, the stirring is discontinued and the liquid separates into two layers. The upper layer of nitroglycerine is run off into an apparatus where it is washed with water until free from acid. The lower layer consists of sulphuric acid and the excess of nitric acid; it is allowed to stand a few days, during which the last traces of nitroglycerine separate out, and after denitration is worked up for sulphuric acid. The nitroglycerine is again washed with aqueous sodium carbonate, and finally dried by filtration through calcined soda.

In the pure state nitroglycerine is a heavy, colourless oil of sp. gr. 1·6. It has a sweet taste and is poisonous, its vapour producing headache, vertigo and loss of consciousness. It is only sparingly soluble in water but dissolves readily in alcohol, benzene and ether. At low temperatures it solidifies to needle-shaped crystals which melt at 11°.

Nitroglycerine burns quietly if ignited in small quantities, but explodes violently when rapidly heated, or on being struck or detonated with mercury fulminate. The decomposition proceeds according to the equation

$$2C_3H_5(ONO_2)_3 = 6CO_2+5H_2O+6N+O$$

In the pure state the compound is not adapted for general use as an explosive, owing to its fluid nature and extreme sensitiveness to mechanical shock. Further, the shattering rapidity with which the explosion is completed renders it useless as a propellant for artillery. In 1867 the Swedish chemist, Alfred Nobel, first showed how nitroglycerine could, by admixture with other substances, be handled and used with safety. When the liquid is mixed with about one-third of its weight of kieselguhr —a fine siliceous earth—it forms a plastic mass of the consistency of putty, known as **dynamite,** from which charges of definite weight are readily made. In this case the kieselguhr functions merely as an indifferent medium of dilution. Apparently the particles of nitroglycerine are separated from one another by the very finely divided kieselguhr, thus slowing down the speed of decomposition and allowing the effect of explosion to be calculated. Further, under ordinary conditions dynamite is not liable to be exploded accidentally. In some countries, notably America, wood pulp or wood powder is substituted for kieselguhr. Dynamite is employed in blasting but not as a propellant for projectiles, since the walls of the gun are not capable of withstanding the sudden impulse. For mining purposes in Great Britain dynamite has very largely been displaced by other mixtures, such as *blasting gelatine* (nitroglycerine with 7 to 10 per cent. of collodion cotton), and *gelignite* or *gelatine dynamite*.

In the year 1889 Nobel succeeded in adapting nitroglycerine for use as a *smokeless propellant powder* by mixing it with nitrocellulose (p. 326). According to Nobel's process, equal parts by weight of these two substances are intimately incorporated with one another, and while the mass

is still plastic it is formed into cubes, rods or other regular shapes. In the product so obtained the components exist in the form of a solid solution, and as a result of the horny consistency of the material it decomposes comparatively slowly on ignition. The best known nitroglycerine powder is *cordite*, composed of 65 per cent. nitrocellulose, 30 per cent. nitroglycerine and 5 per cent. vaseline.

Nitroglycerine is also utilised to a small extent in medicine for asthma, and in cases of poisoning by carbon monoxide or coal gas.

III.—HIGHER POLYHYDRIC ALCOHOLS[1]

A representative of the **tetrahydric alcohols** has long been known in **erythritol,** $CH_2OH.CHOH.CHOH.CH_2OH$, which occurs in the free state in nature and in the form of *erythrin* (the erythritol ester of orsellinic acid) in many lichens and algæ. The natural product is the inactive modification, identical with that obtained by the reduction of *d*-erythrose. Erythritol forms large clear crystals of m.p. 120° and has a very sweet taste. It dissolves readily in water, only with difficulty in ordinary alcohol, and not at all in ether. Its constitution as a normal straight chain derivative follows from its conversion into *n*-secondary butyl iodide on reduction with hydriodic acid.

$$CH_2OH.CHOH.CHOH.CH_2OH \longrightarrow CH_3.CHI.CH_2.CH_3$$

Nitric acid converts it into the nitric ester, $C_4H_6(ONO_2)_4$, also known as *nitro-erythritol*, which like nitroglycerine is a powerful explosive. On oxidation it yields first *erythrose*, a mixture of the monoaldehyde, $CH_2OH.CHOH.CHOH.CHO$, and the ketone $CH_2OH.CHOH.CO.CH_2OH$, and finally *erythronic acid* (trihydroxy butyric acid), $CH_2OH.CHOH.CHOH.COOH$.

Among the **pentahydric alcohols** or pentitols the best known representatives are **arabitol, xylitol** and **adonitol.** These all possess the constitutional formula $CH_2OH.CHOH.CHOH.CHOH.CH_2OH$, containing two asymmetric carbon atoms, and are stereoisomeric with one another. A homologue of this series is **rhamnitol,** $CH_3.(CHOH)_4.CH_2OH$, which is formed by the reduction of rhamnose.

Hexitols, or **hexahydric alcohols,** are of importance not only because they occur extensively in nature, but also on account of their close relationship to the simple class of sugars known as hexoses. The latter are aldehydes or ketones corresponding to the hexahydric alcohols, into which they may be converted by reduction with sodium amalgam. Considering their similarity in structure, it is not surprising to find that the hexitols and the hexoses possess many properties in common, such as sweet taste and solubility in water. Three alcohols of this class may be mentioned, **mannitol, dulcitol and sorbitol,** which are all stereoisomerides of the formula

$$CH_2OH.CHOH.CHOH.CHOH.CHOH.CH_2OH$$

[1] These contain asymmetric atoms, which are indicated in the formulæ by heavier type.

Ordinary or *d*-**mannitol** occurs widely distributed in the vegetable kingdom, being found especially in manna, the evaporated sap of the manna tree. It is prepared from this source by extraction with hot alcohol and subsequent crystallisation. It is also formed during the mucous fermentation of cane sugar, and may be obtained artificially by reducing *d*-mannose or *d*-fructose with sodium amalgam.

$$C_6H_{12}O_6+2H = C_6H_{14}O_6$$

d-Mannitol crystallises in needles or prisms melting at 166°.

l-*Mannitol* and r-*mannitol* are obtained by the reduction of *l*- and *r*-mannose respectively. *r*-Mannitol was the starting-point in E. Fischer's synthesis of glucose and fructose.

Dulcitol, m.p. 188°, is optically inactive and occurs chiefly in dulcite manna, from which it is prepared. It is also formed by the reduction of lactose and of *d*-galactose.

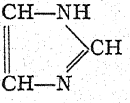
d-**Sorbitol,** $C_6H_{14}O_6+H_2O$, is present in the berry of the mountain ash, and is formed by the reduction of glucose, or together with mannitol from fructose. The anhydrous compound melts at 110°.

XIII

Dialdehydes and Diketones

These interesting compounds are valuable starting-points for the synthesis of various cyclic derivatives. They may be prepared by the catalytic reduction of the corresponding acid chlorides,[1] using hydrogen in the presence of finely divided palladium. Only two of the **dialdehydes,** namely glyoxal and succindialdehyde, will be dealt with here.

Glyoxal, *oxaldehyde, diformyl,* O : CH.CH : O, is formed by the cautious oxidation of ethylene glycol, ethyl alcohol, or acetaldehyde with nitric acid, and exists in four modifications.[2] **Poly-glyoxal** $[(CHO)_2]_n$, the first of these to be known, was discovered in 1865 by Debus, and is the form obtained by the above methods of preparation. **Monomolecular glyoxal,** CHO.CHO, was first isolated by heating poly-glyoxal with phosphorus pentoxide. It is a solid which melts at 15° to a yellow liquid of b.p. 51°. The vapour possesses an intense emerald green colour, and on condensation yields at first a green liquid. This substance can only be preserved for a few hours, and even when kept in a strong freezing mixture rapidly polymerises to **para-glyoxal,** an insoluble modification of unknown molecular weight. A solid **trimolecular form** $[(CHO)_2]_3$ has also been discovered, which in the anhydrous state is readily soluble and differs from the variety found by Debus in rapidly reducing Fehling's solution. As would be expected, glyoxal possesses a strong aldehydic character. It combines, for example, with two molecules of sodium bisulphite to give crystalline glyoxal sodium bisulphite, $C_2H_2O_2(SO_3HNa)_2+H_2O$, by means of which it is usually isolated. With concentrated ammonia glyoxal yields, among other products, a cyclic base **glyoxaline,** of the formula



which melts at 90° and boils at 263°. This is the parent substance of the *glyoxalines* or *iminazoles,* and is of importance in connection with the constitution of the alkaloid pilocarpine and of certain other natural products.

[1] K. W. Rosenmund and co-workers, *Ber.*, 1921, **54**, 2888; 1922, **55**, 609. [2] Harries, *Ber.*, 1907, **40**, 165.

Succindialdehyde, $CHO.CH_2.CH_2.CHO$, is formed when succindialdoxime—obtained by the interaction of pyrrole and hydroxylamine—is treated in aqueous suspension with nitrous acid; it may also be obtained from diallyl, $CH_2:CH.CH_2.CH_2.CH:CH_2$, by treatment with ozone.[1] Diallyl is prepared by the action of sodium on allyl iodide. From the latter reaction it follows that diallyl is 1 : 5-hexadiene.

$$\begin{matrix}CH_2.CH:NOH\\ |\\ CH_2.CH:NOH\end{matrix} + \begin{matrix}HNO_2\\ HNO_2\end{matrix} = \begin{matrix}CH_2.CHO\\ |\\ CH_2.CHO\end{matrix} + 2N_2O + 2H_2O$$

Succindialdoxime — Succindialdehyde.

$$H_2C:CH.CH_2.CH_2.CH:CH_2 \xrightarrow{\text{Ozone.}}$$

Diallyl (1 : 5-hexadiene)

$$H_2C\begin{matrix}O\\ O.O\end{matrix}CH.CH_2.CH_2.CH\begin{matrix}O\\ O.O\end{matrix}CH_2 \xrightarrow[\text{with water.}]{\text{Heating}} O:CH.CH_2.CH_2.CH:O$$

Diallyl diozonide. — Succindialdehyde.

The *diacetal of succindialdehyde* is produced during the electrolysis of the potassium salt of β-diethoxy-propionic acid,

$$\begin{matrix}K\\ K\end{matrix}\Big|O.CO.\Big|CH_2.CH(OC_2H_5)_2 + 2H_2O =$$

$$\begin{matrix}CH_2.CH(OC_2H_5)_2\\ |\\ CH_2.CH(OC_2H_5)_2\end{matrix} + 2KOH + 2CO_2 + H_2$$

Diacetal of succindialdehyde.

On hydrolysis, the acetal yields the free dialdehyde.

Succindialdehyde exists in a monomolecular liquid form and in a polymeric vitreous modification. The former is a colourless oil, b.p. 56°/8·5 mm., which very readily undergoes polymerisation.

By means of succindialdehyde it is possible to pass in a simple manner from an aliphatic compound to the three typical heterocylic compounds furane, pyrrole and thiophene.

$$\begin{matrix}CH_2—CHO\\ |\\ CH_2—CHO\end{matrix}$$

Elimination of H_2O → $\begin{matrix}CH=CH\\ |\quad\quad\rangle O\\ CH=CH\end{matrix}$ Furane.

Warming with NH_3 → $\begin{matrix}CH=CH\\ |\quad\quad\rangle NH\\ CH=CH\end{matrix}$ Pyrrole.

Heating with P_2S_5 → $\begin{matrix}CH=CH\\ |\quad\quad\rangle S\\ CH=CH\end{matrix}$ Thiophene.

[1] Harries, *Ann.*, 1905, **343**, 311.

For an example of its use in synthesising still more complex heterocyclic compounds, see *tropinone*, p. 726 (R. Robinson, *J. C. S.*, 1917, III, 762).

DIKETONES

Nomenclature.—According to the relative positions of the >CO groups, these compounds are distinguished as α- or 1 : 2-diketones containing the group CO.CO; β- or 1 : 3-diketones containing the group $CO.CH_2.CO$; γ- or 1 : 4-diketones containing the group $CO.CH_2.CH_2.CO$, and so on. In some cases names are also in common use which represent α-ketones as formed by the union of two acid radicals R.CO—, and β-ketones as acyl-substituted ketones, *e.g.* diacetyl, $CH_3.CO.CO.CH_3$, and acetyl-acetone, $CH_3.CO.CH_2.CO.CH_3$.

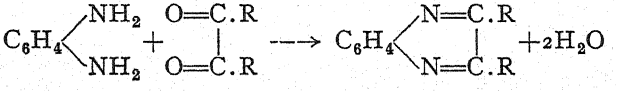
According to the Geneva nomenclature, the diketones are named after the corresponding hydrocarbon by adding the termination -dione, *e.g.* acetyl-acetone or 2 : 4-pentane-dione.

1. α- or 1 : 2-Diketones

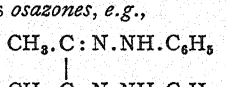
The α-diketones are yellow, volatile liquids of pungent smell, which are obtained from their monoximes, the isonitroso-ketones, by boiling with dilute sulphuric acid.[1] *Isonitroso-ketones* are prepared by the action of nitrous acid on ketones.

$$\underset{\text{Methyl ethyl ketone}}{CH_3.CO.CH_2.CH_3} \xrightarrow{HNO_2} \underset{\substack{\text{Isonitroso methyl ethyl ketone}\\ \text{(Diacetyl monoxime)}}}{CH_3.CO.C(NOH).CH_3} \longrightarrow \underset{\text{Diacetyl.}}{CH_3.CO.CO.CH_3}$$

α-Diketones condense with *o*-phenylene diamines to form cyclic compounds known as *quinoxalines*.



With hydroxylamine the α-diketones yield monoximes (isonitroso-ketones) as well as dioximes (*glyoximes*). Phenyl hydrazine forms monohydrazones and dihydrazones, the latter also being known as *osazones*, *e.g.*,



Diacetyl osazone.

Diacetyl, *diketo-butane*, $CH_3.CO.CO.CH_3$, is obtained by the method described above.[2] It is a yellow liquid of penetrating smell and b.p. 88°, the vapour of which possesses the colour of chlorine. With hydrogen peroxide it is readily decomposed into two molecules of acetic acid.

$$CH_3.CO.CO.CH_3 + HO.OH = 2CH_3.CO.OH$$

[1] For further methods of preparation see Pauly, *Ber.*, 1901, **34**, 2092. Tschugaeff, *Ber.*, 1907, **40**, 186. [2] Diels, *Ber.*, 1907, **40**, 4336.

Diacetyl, like the simple aldehydes and ketones, is easily reduced by biochemical means, *e.g.* in the presence of fermenting yeast. In this case *l*-rotatory 2 : 3-butylene-glycol is obtained.[1]

Diacetyl dioxime, dimethyl glyoxime, $CH_3.C(NOH).C(NOH).CH_3$ is conveniently prepared by the action of hydroxylamine on the monoxime, formed as described above from methyl ethyl ketone and nitrous acid.[2] It gives a dark red precipitate with solutions of nickel salts, and is used for the qualitative and quantitative determination of this metal.

2. β- or 1 : 3-Diketones

Preparation.—β-Diketones are usually obtained by the condensation of esters with ketones, a reaction of general application discovered by Claisen. It should be noted that esters can also be condensed with esters, in which case β-ketonic esters of the general formula $R.CO.CH_2.COOR$ are obtained. This reaction, known as the *Claisen condensation*,[3] involves the elimination of alcohol between the group $R.COOC_2H_5$ of an ester and the $CH_3.CO—$ of a ketone (or the $R.CH_2.CO—$ of a second ester molecule), and may be effected by means of the following reagents : 1. an alcoholic solution of sodium ethoxide ; 2. alcohol-free sodium ethoxide ; 3. metallic sodium ; or 4. sodamide. The classical prototype of this condensation is the conversion of ethyl acetate into aceto-acetic ester, and the course of the reaction will be discussed under this substance.

Acetyl-acetone, $CH_3.CO.CH_2.CO.CH_3$, is prepared by condensing acetic ester with acetone in the presence of one of the above agents,[3] *e.g.* metallic sodium. The sodium salt of acetyl-acetone so obtained is then converted into the insoluble copper salt, from which the free ketone is liberated by treatment with dilute sulphuric acid.

$$\underset{\text{Acetic ester}}{CH_3.CO.OC_2H_5}+\underset{\text{Acetone.}}{H_3C.CO.CH_3}$$

$$\longrightarrow CH_3.C(ONa):CH.CO.CH_3 \longrightarrow \underset{\text{Acetyl-acetone.}}{CH_3.CO.CH_2.CO.CH_3}$$

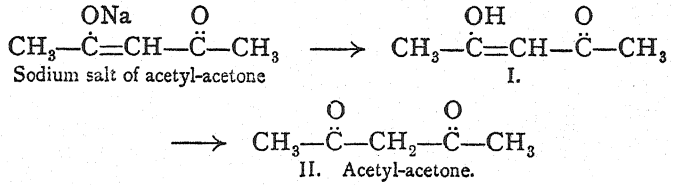
It is a colourless, pleasant-smelling liquid, b.p. 137°. When boiled with water it decomposes into acetone and acetic acid.

$$CH_3.CO.CH_2.CO.CH_3+HOH = CH_3.CO.CH_3+CH_3.COOH$$

Constitution and Properties of the β-Diketones.—The β-diketones possess an acidic character as shown by the formation of metallic derivatives, many of which are insoluble in water but soluble in benzene, chloroform and other organic solvents. Characteristic copper salts are also formed which are only sparingly soluble in water. In general it is assumed

[1] C. Neuberg and F. F. Nord, *Ber.*, 1919, **52**, 2248. [2] *J. pr. Ch.* (2), 1908, **77**, 414. *C.*, 1919, **III**, 43. W. L. Semon, *J. Am. C. S.*, 1925, **47**, 2033. [3] Claisen, *Ber.*, 1889, **22**, 1009; 1905, **38**, 709.

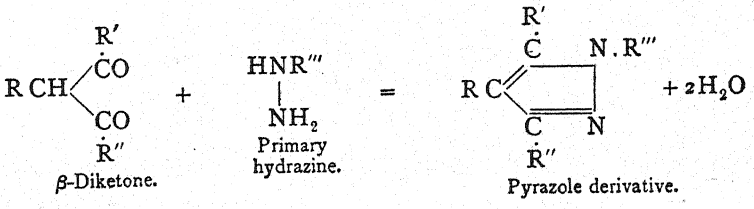
that the metal is united to oxygen, *i.e.*, that the salts are derived from the acidic or enol form I., while the free ketones may represent equilibrium



mixtures of the keto and enol forms (*cf.* p. 68), although they are usually written as diketo-compounds II.

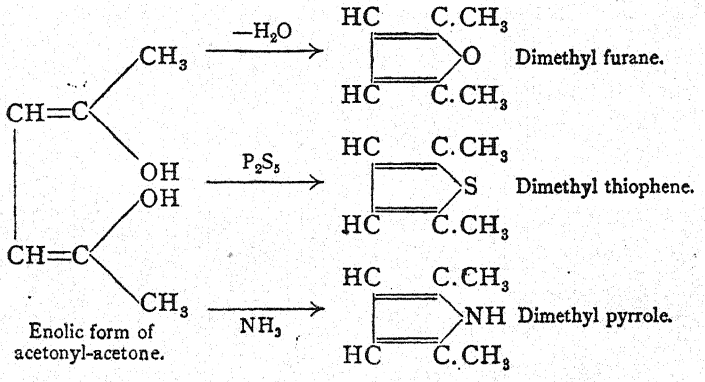
The *enol form of acetyl-acetone* I. has been isolated in the pure state by crystallising the equilibrium mixture from petroleum ether at a low temperature.[1] A more convenient method of preparation is to distil the mixture from a glass flask,[2] when the traces of alkali from the glass catalytically convert the greater part of the keto into the enol form. The distillate contains about 99 per cent. enol form.

Among the great number of condensations undergone by β-diketones, one deserving special mention is their reaction with hydrazines to give *pyrazole derivatives*. This reaction is the most useful of all methods for the preparation of pyrazoles, and may be formulated as follows :



3. γ- or 1 : 4-Diketones

A compound of this type is **acetonyl-acetone,** 2 : 5-*hexane-dione*, $CH_3.CO.CH_2.CH_2.CO.CH_3$, which is conveniently prepared from β-diaceto-succinic ester by boiling with sodium hydroxide. It is a clear, pleasant-smelling liquid, b.p. 191° under 750 mm., which dissolves readily in water, alcohol and ether.



[1] L. Knorr and H. Fischer, *Ber.*, 1911, 44, 2771. [2] K. H. Meyer and Hopff, *Ber.*, 1921, 54, 579.

The *γ-diketones* are readily converted into derivatives of furane, thiophene and pyrrole (see formulæ at bottom of previous page).

Many pyrrole derivatives have the property of colouring a pine shaving intensely red, a reaction which has been proposed as a test for 1 : 4-diketones. L. Knorr[1] recommends the following procedure: a small amount of the substance to be tested is dissolved in glacial acetic acid, a solution of ammonia in excess of acetic acid is added and the mixture boiled for about half a minute, after which it is treated with dilute sulphuric acid and again boiled while a splint of pinewood is held in the vapour. An intense reddening of the splint shows the presence of a 1 : 4-diketone in the solution. Since, however, this colour reaction may be brought about by other compounds besides pyrroles, it should be used with caution.

Tautomerism of the Triketones

As will be seen later in the case of aceto-acetic ester, those compounds containing the group $CO.CH_2.CO$ react on the one hand as if this group were actually present, and on the other as though they contained the complex $C(OH):CH.CO$. In other words, they behave at times as genuine ketones and at others as enolic or *aci*-ketones. In the case of the *β*-diketones discussed above, no representative of the class has so far been isolated in both forms.

The triketones, however, are capable of existing in the free state in the keto form (I) as well as in the enol form (II), as has been shown by the investigations of Claisen.[2]

I. $H-C(CO-R)(CO-R')(CO-R'')$ Keto form (*β*)

II. $C(C(OH)-R)(CO-R')(CO-R'')$ Enol or *aci*-form (*α*).

From the above formulæ it may be seen that this peculiar form of isomerism (tautomerism) depends only on the movement of a hydrogen atom within the molecule. The compounds are therefore very labile, and it has not been found possible to prove the existence of both types in all substances of this class.

Claisen has suggested that the tendency to give the enol form increases as the acyl groups attached to the methane carbon atom become more numerous or more acidic in character. Since the acetyl group, $CO.CH_3$, is more acidic than the benzoyl group, COC_6H_5, it should be found that in the series

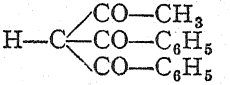
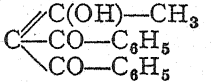
$$CHA_3,\ CHA_2B,\ CHAB_2,\ CHB_3$$

(A=acetyl, B=benzoyl) the tendency towards the enol form should steadily diminish. In actual fact *triacetyl-methane* and *diacetyl-benzoyl-methane* are only known in the enolic modifications,

$C(C(OH)-CH_3)(CO-CH_3)(CO-CH_3)$ $\qquad$ $C(C(OH)-CH_3)(CO-CH_3)(CO-C_6H_5)$

[1] Knorr, *Ber.*, 1886, **19**, 46. See also C. Neuberg, *C.*, 1904, **II**, 1435. [2] *Ber.*, 1894, **27**, 14; *Ann.*, 1896, **291**, 25. Claisen and Haase, *Ber.*, 1903, **36**, 3674.

whereas *dibenzoyl-acetyl-methane* has been isolated in both forms.

In *tribenzoyl-methane* the α- or enolic form has already become so labile as to transform itself with extraordinary ease into the β- or keto-compound. The degree of stability of the two forms of a triketone depends therefore on the nature of the acid radicals present.

In the case of the triketones, Claisen was also able to show how the keto and enol (*aci*-ketonic) forms differ in chemical behaviour. The genuine ketones I are indifferent towards alkalis and ferric chloride, neither dissolving in the former nor giving any colour with the latter. The enols, on the other hand, are directly soluble in alkalis with the formation of salts. They also give intense colorations with ferric chloride, a reaction which is sometimes a convenient means of rapidly distinguishing between keto and enol forms, and of following experimentally the transformation of the one into the other.

The conversion of the keto into the enol form is brought about by treatment with alkalis. In the presence of solvents, or in the fused state, either form is converted into an equilibrium mixture of isomerides in which the relative proportion of the two forms depends on various factors, such as the nature of the solvent and the temperature.

XIV

Monobasic Aldehydic and Ketonic Acids

These acids may be regarded as oxidation products of the hydroxy-acids (see p. 233) and might have been treated in connection with the latter. In the ease with which they are converted into cyclic derivatives, however, and in the frequent occurrence of isomerism, they show many resemblances to dialdehydes and diketones, and it is more convenient to discuss them at this stage. As might be expected, these acids possess the dual character of carboxylic acids and of aldehydes or ketones.

Glyoxalic acid, *glyoxylic acid*, $CHO.COOH+H_2O$, is the best known aldehydic acid. It occurs in young plants and unripe fruit (*e.g.* gooseberries and currants), and can be formed by the oxidation of ethyl alcohol with nitric acid. It may be obtained synthetically from dichloroacetic acid by heating with water. As in the similar case of chloral hydrate, it is assumed by many chemists that glyoxalic acid exists in chemical combination with the molecule of water which it contains according to the above formula, and thus possesses the structure of dihydroxyacetic acid, $CH(OH)_2.COOH$. In this connection Debus, who discovered the compound, proposed the retention of the formula $CHO.COOH+H_2O$ as being sufficient to explain all its properties. Glyoxalic acid gives the usual reactions of aldehydes, reducing ammoniacal silver solutions,

combining with sodium bisulphite, and forming an oxime. When boiled with alkalis it yields glycollic acid and oxalic acid.

$$2\,\begin{vmatrix}\text{COOH}\\ \text{CHO}\end{vmatrix} + H_2O = \begin{vmatrix}\text{COOH}\\ \text{CH}_2\text{OH}\end{vmatrix} + \begin{vmatrix}\text{COOH}\\ \text{COOH}\end{vmatrix}$$

Formyl-phenylacetic ester is obtained by the condensation of ethyl formate with phenylacetic ester.[1]

$$\underset{\text{Ethyl formate}}{H.CO.OC_2H_5} + \underset{\text{Phenylacetic ester}}{CH_2(C_6H_5).COOC_2H_5} \longrightarrow \underset{\text{Formyl-phenylacetic ester.}}{H.CO.HC(C_6H_5).COOC_2H_5} + C_2H_5OH$$

This compound undergoes interesting tautomeric changes similar to those observed in the case of diketones and ketonic esters (see diaceto-succinic ester).

Ketonic acids are of more importance than aldehydic acids. Like the diketones (p. 255) they are distinguished as α-, β-, γ- or δ-keto-acids according to the position of the >CO group with regard to the carboxyl. They are generally named as acyl-substituted fatty acids, or after the Geneva nomenclature by adding the word "acid" to the name of the parent ketone, *e.g.*,

$CH_3.CO.CO_2H$	$CH_3.CO.CH_2.CO_2H$	$CH_3.CO.CH_2.CH_2.CO_2H$
α-Keto-propionic acid,	β-Keto-butyric acid,	γ-Keto-valeric acid.
Acetyl-formic acid,	Acetoacetic acid,	β-Acetyl-propionic acid,
Propanone acid,	Butane-3-one-1-acid.	Pentane-4-one-1-acid.

The α- and γ-keto-acids are stable even in the free state, but the free β-keto-acids readily undergo decomposition.

In the protein metabolism of the living organism α-ketonic acids are formed by the oxidative deamination of α-amino-acids. This is the commonest method by which amino-acids are decomposed in the animal body. It is assumed that an α-hydroxy-α-amino-acid occurs as an intermediate.

$$\begin{vmatrix}\text{CH}_3\\ \text{CHNH}_2\\ \text{COOH}\end{vmatrix} \xrightarrow{+O} \begin{vmatrix}\text{CH}_3\\ \text{C(OH)(NH}_2\text{)}\\ \text{COOH}\end{vmatrix} \xrightarrow{-NH_3} \begin{vmatrix}\text{CH}_3\\ \text{CO}\\ \text{COOH}\end{vmatrix}$$

Pyruvic acid, pyro-racemic acid, *acetyl-formic acid*, $CH_3.CO.COOH$, is the simplest α-keto-acid, and is prepared by distilling tartaric acid with potassium hydrogen sulphate (hence the name). It may be synthesised by the hydrolysis of acetyl cyanide.

$$CH_3.CO.Cl \xrightarrow{KCN} CH_3.CO.CN \xrightarrow{H_2O} CH_3.CO.COOH$$

α-Ketonic acids, in general, are prepared by hydrolysing the nitriles obtained by treating acid chlorides with potassium cyanide. This method of preparation also confirms their constitution as α-keto-acids.

Pyruvic acid is a colourless liquid of pungent smell, miscible in all

[1] Wislicenus, *Ann.*, 1896, **291**, 147; 1912, **398**, 265.

proportions with water, alcohol and ether. It solidifies at low temperatures, melts again at 9°, and boils at 165° with partial decomposition. It shows the reactions of a ketone in addition to those of an acid, forming an oxime and a hydrazone and combining with HCN. Like other ketones it also undergoes condensation, yielding a benzene derivative (*uvitic acid*).

Methylglyoxal, *pyruvic aldehyde*, $CH_3.CO.CHO$, is the simplest example of a keto-aldehyde. It may be obtained by hydrolysing iso-nitrosoacetone with dilute sulphuric acid. When heated to 100° with water, or more rapidly and completely on standing with cold dilute alkali, methylglyoxal is converted into lactic acid.

Methylglyoxal may also be prepared from acetone in good yield by heating it with selenium dioxide, which is a specific reagent for effecting oxidations of the general types $R.CH_2.CHO \rightarrow R.CO.CHO$ and $R.CH_2.CO.R' \rightarrow R.CO.CO.R'$. During the reaction metallic selenium is precipitated.[1]

A considerable amount of attention has recently been directed towards pyruvic acid and its aldehyde in connection with physiological processes. In the living organism pyruvic acid may be transformed into alanine, lactic acid, acetoacetic acid or acetaldehyde, all of these changes being equilibrium reactions. Pyruvic acid is thus assigned a central position in the conversion of the various constituents of the body (proteins, carbohydrates, fats) into one another [2] (see also p. 306). The rôle of the acid and its aldehyde in alcoholic fermentation has been investigated carefully by Neuberg [3] (p. 149). In this connection Abderhalden states that there is no longer any doubt that compounds of three carbon atoms (pyruvic acid, lactic acid, glyceric aldehyde and pyruvic aldehyde, etc.) form the common channel through which the carbohydrates, fats and proteins or amino-acids are mutually interconvertible.

Acetoacetic acid, *β-keto-butyric acid*, $CH_3.CO.CH_2.COOH$, is prepared from its esters by hydrolysis with cold dilute alkali. It is obtained on acidification as a viscous liquid, which very readily decomposes into acetone and carbon dioxide. Acetoacetic acid occurs in the urine of diabetic patients, and is an important decomposition product of fatty acids in the organism. Otherwise the free acid is of little interest.

Acetoacetic ester, $CH_3.CO.CH_2.COOC_2H_5$, was discovered in the year 1863 by Geuther. It is prepared by the condensation of ethyl acetate in the presence of sodium.

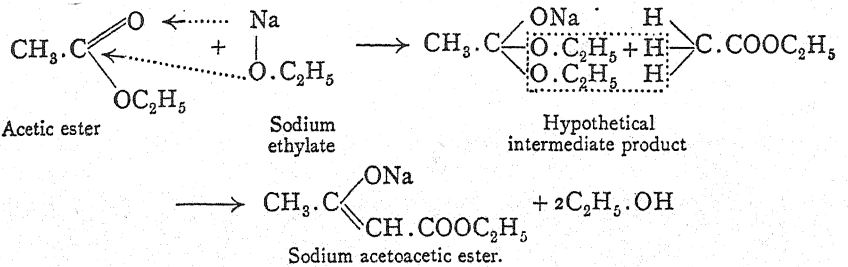
Metallic sodium is added to purified ethyl acetate, when a reaction gradually sets in, as shown by the evolution of hydrogen and the boiling of the liquid. After all the sodium has dissolved, the mixture contains excess of ethyl acetate together with sodium ethoxide and sodium acetoacetic ester. The two latter compounds separate out as a paste. Free acetoacetic ester is liberated by the addition of dilute acetic acid, and forms an oily layer above the aqueous liquid. It is removed and, without previous drying, is purified by fractional distillation.

Claisen in 1887 advanced the view that the formation of sodium acetoacetic ester is not induced primarily by the action of sodium but by

[1] H. L. Riley, J. F. Morley and N. A. C. Friend, *J. C. S.*, **1932**, 1875. [2] Wieland and A. Wingler, *Ann.*, 1924, **436**, 229. [3] *Ber.*, 1920, **53**, 1039; 1924, **57**, 1436. Also "Die Gärungsvorgänge und die Zuckerumsatz der Zelle."

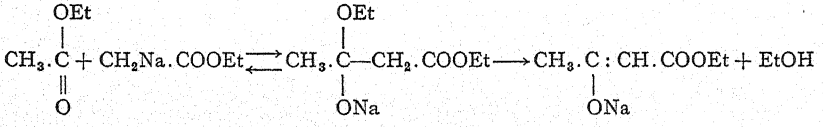
sodium ethoxide produced from alcohol contained as an impurity in the acetic ester employed. In later stages of the reaction more alcohol is liberated, which combines with the sodium present to yield more ethoxide. The formation of acetoacetic ester can also be effected by use of sodamide in place of sodium or sodium ethoxide.

Claisen's theory of the acetoacetic ester reaction is expressed in the following scheme.



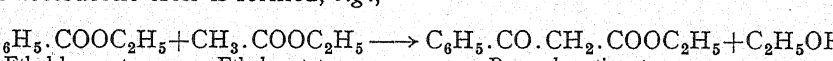
Acetic ester — Sodium ethylate — Hypothetical intermediate product — Sodium acetoacetic ester.

A number of other mechanisms have recently been suggested for this reaction such as that due to Arndt and Eistert,[1] in which the first stage is the reversible addition of sodium acetic ester to the CO-group of a molecule of ethyl acetate. This is followed by irreversible decomposition of the addition compound under the influence of alkali to yield sodium acetoacetic ester together with a proton and an ethoxy anion, which unite forming alcohol.



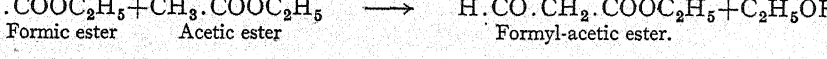
The acetoacetic ester condensation is the prototype of a large number of similar reactions, some of which have already been described on p. 256. These condensations are of great value in synthetic chemistry, and may be further illustrated by the following examples taken from the investigations of Claisen and Wislicenus.

When sodium ethoxide is allowed to interact with a mixture of two esters of monobasic acids, a ketonic ester of constitution similar to that of acetoacetic ester is formed, *e.g.*,



Ethyl benzoate — Ethyl acetate — Benzoyl-acetic ester.

If one of the reacting esters is ethyl formate, an ester of an aldehydic acid is obtained :



Formic ester — Acetic ester — Formyl-acetic ester.

[1] F. Arndt and B. Eistert, *Ber.*, 1936, 69, 2381. See, however, H. B. Watson, *Ann. Rep.* 1939, 212, where a review of this and other theories will be found.

The use of a mixture of ethyl acetate (1 mol.) and an ester of a dicarboxylic acid (1 mol.) leads to the formation of keto-dicarboxylic esters :

$$\begin{matrix} COOC_2H_5 \\ | \\ COOC_2H_5 \\ \text{Ethyl oxalate} \end{matrix} + H_3C.COOC_2H_5 \longrightarrow \begin{matrix} CO.CH_2.COOC_2H_5 \\ | \\ COOC_2H_5 \\ \text{Oxalo-acetic ester.} \end{matrix} + C_2H_5OH$$

Ethyl acetate

Finally, as has already been mentioned on p. 256, one molecule of ester may be replaced by one molecule of a ketone, with the formation of polyketones and keto-aldehydes :

$$\underset{\text{Ethyl acetate}}{CH_3.COOC_2H_5} + \underset{\text{Acetone}}{H_3C.CO.CH_3} \longrightarrow \underset{\text{Acetyl-acetone.}}{CH_3.CO.CH_2.CO.CH_3} + C_2H_5OH$$

$$\underset{\text{Formic ester}}{H.COOC_2H_5} + \underset{\text{Acetone}}{H_3C.CO.CH_3} \longrightarrow \underset{\text{Formyl-acetone.}}{H.CO.CH_2.CO.CH_3} + C_2H_5OH$$

Negatively-substituted β-ketonic acids may be synthesised by the action of negatively substituted aldehydes on diazo-acetic ester. In this manner *γ-trichloro-acetoacetic ester* is obtained from chloral :—

$$\begin{matrix} CCl_3 \\ | \\ CHO \end{matrix} + \begin{matrix} CO.OC_2H_5 \\ | \\ N_2CH \end{matrix} \longrightarrow \begin{matrix} CCl_3 \\ | \\ CO.CH_2.COOC_2H_5 \end{matrix} + N_2$$

Acetoacetic Ester and its Synthetic Reactions

Acetoacetic ester is a colourless, pleasant-smelling liquid, b.p. 181°, which is sparingly soluble in water and gives a deep violet coloration with ferric chloride.[1]

Owing to its great reactivity it is to be classed as one of the most important organic compounds, from which a large number of other substances may be prepared. The utility of acetoacetic ester as a synthetic reagent depends partly on the ease with which one of the hydrogen atoms may be replaced by sodium. When allowed to interact with metallic sodium an evolution of hydrogen occurs with the simultaneous formation of a sodium salt :

$$CH_3.CO.CH_2.COOC_2H_5 + Na \longrightarrow H + CH_3.C(ONa) : CH.CO_2C_2H_5$$

The sodium salt is more conveniently prepared by treating the ester with an alcoholic solution of sodium ethoxide.

By making use of this sodium compound a variety of groups can be introduced into the acetoacetic ester molecule. On bringing it into reaction with an organic halogen compound a separation of sodium halide takes place and the two organic radicals unite together. In the following examples the sodium derivative is written as $CH_3.CO.CHNa.COOC_2H_5$ in order to abbreviate and simplify the equations—although the con-

[1] For a characteristic colour reaction of quinones with acetoacetic ester and other compounds containing a similarly attached methylene group see W. Kesting, *Ber.*, 1929, **62**, 1422.

stitution of the metallic compound is probably more accurately expressed by the enolic formula.

$$CH_3.CO.CHNa.COOC_2H_5 + I.CH_3 = CH_3.CO.\underset{\underset{\text{Methyl-acetoacetic ester}}{CH_3}}{CH}.COOC_2H_5 + NaI$$

$$CH_3.CO.CHNa.COOC_2H_5 + Cl.COCH_3 = CH_3.CO.\underset{\underset{\text{Acetyl-acetoacetic ester}}{CH_3.CO}}{CH}.COOC_2H_5 + NaCl$$

(Acetyl chloride)

$$CH_3.CO.CHNa.COOC_2H_5 + Cl.CH_2.COOC_2H_5 =$$

(Chloro-acetic ester.[1])

$$CH_3.CO.\underset{\underset{\text{Aceto-succinic ester.}}{CH_2.COOC_2H_5}}{CH}.COOC_2H_5 + NaCl$$

These mono-substituted esters also react with sodium ethoxide to give sodium derivatives, which by interaction with an organic halogen compound yield disubstituted acetoacetic esters, *e.g.*,

$$CH_3.CO.\underset{\underset{\text{Sodium methyl-acetoacetic ester}}{CH_3}}{CNa}.COOC_2H_5 + BrC_3H_7 = CH_3.CO.\underset{\underset{\text{Methyl-propyl-acetoacetic ester.}}{CH_3\ C_3H_7}}{C}.COOC_2H_5 + NaBr$$

(Propyl bromide)

The great synthetic value of acetoacetic ester lies less in the production of the above types of compounds than in the simpler substances to which they give rise on hydrolysis. Acetoacetic ester may be hydrolysed in two ways, which are distinguished according to the nature of the product as **"ketonic hydrolysis"** (I) and **"acid hydrolysis"** (II) respectively.

I. $$CH_3.CO.CH_2.COOC_2H_5 + HOH = \underset{\text{Acetone}}{CH_3.CO.CH_3} + CO_2 + C_2H_5.OH$$

II. $$CH_3.CO.CH_2.COOC_2H_5 + 2HOH = 2\underset{\text{Acetic acid.}}{CH_3.COOH} + C_2H_5.OH$$

Ketonic hydrolysis occurs chiefly on treatment with hot dilute acids [2] or alkalis, or by heating with water in a closed tube to 200°, whereas acid hydrolysis is brought about by heating with concentrated alkalis. Since the above-mentioned derivatives of the ester can also be hydrolysed in a similar manner to yield ketones or acids, we have here a *general method for the preparation of mono- and di-substituted methyl ketones* of the type of $R.CH_2.CO.CH_3$ and $RR'CH.CO.CH_3$, *and of mono- and di-substituted acetic acids* $R.CH_2.COOH$ and $RR'CH.COOH$.

The *electrolytic reduction* of acetoacetic ester or its substitution products leads to the formation of hydrocarbons, *e.g.* butane from aceto-acetic ester itself.

$$CH_3.CO.CH_2.COOC_2H_5 \longrightarrow CH_3.CH_2.CH_2.CH_3$$

[1] In the presence of weakly dissociating solvents, addition products can be isolated from chloroacetic ester and sodium acetoacetic ester or its alkyl derivatives. (Michael, *Ber.*, 1905, **38**, 3217.) [2] According to Dehn and Jackson, *J. A. C. S.*, 1933, **55**, 4284, very high yields of ketones may be obtained by use of phosphoric acid.

Two molecules of acetoacetic ester may also be coupled up with one another (*a*) directly, by the action of iodine on sodium acetoacetic ester; (*b*) indirectly through various divalent radicals, by the condensation of acetoacetic ester with aldehydes or alkylene bromides. In case (*a*) the interesting substance *diaceto-succinic ester* is formed; this has been isolated in several dynamic isomerides, the study of which has been of considerable value in connection with the theory of tautomerism. On ketonic hydrolysis it yields acetonyl-acetone (p. 257).

$$\begin{matrix} CH_3—CO—CHNa—COOC_2H_5 \\ CH_3—CO—CHNa—COOC_2H_5 \end{matrix} +2I = \begin{matrix} CH_3—CO—CH—COOC_2H_5 \\ | \\ CH_3—CO—CH—COOC_2H_5 \end{matrix} +2NaI$$

Diaceto-succinic ester (keto-form).

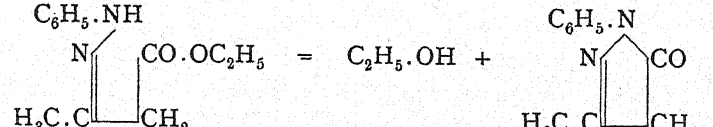
In case (*b*) acetoacetic ester derivatives are produced of the general formula

$$\begin{matrix} CH_3—CO—CH—COOC_2H_5 \\ | \\ CH—R \\ | \\ CH_3—CO—CH—COOC_2H_5 \end{matrix}$$

Compounds of this type were first prepared by Hantzsch and Knoevenagel, and have also proved of interest in the development of the theory of tautomerism.

Finally, it should be noted that *acetoacetic ester unites with certain nitrogen compounds* such as ammonia,[1] amines, hydrazines and hydroxylamine. These reactions are of great importance for the synthesis of a variety of heterocyclic compounds, as may be seen from the following examples.

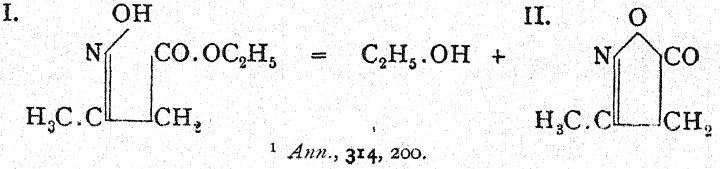
With hydrazine and its monosubstitution products acetoacetic ester yields *pyrazolones*. By making use of phenyl-hydrazine, Knorr in 1883 succeeded in isolating the first pyrazole derivative, 1-phenyl-3-methyl-5-pyrazolone, which forms the starting-point in the technical preparation of antipyrine. The reaction takes place in two phases, the hydrazone of the ester being first obtained and alcohol subsequently eliminated.



Phenyl-hydrazone of acetoacetic ester

1-Phenyl-3-methyl-5-pyrazolone.

Hydroxylamine interacts with acetoacetic ester to form β-iso-nitroso-butyric ester (I), which is readily transformed into *methyl-isoxazolone* (II).



[1] *Ann.*, 314, 200.

By condensation with urea there is obtained *methylurazil*,

$$H_3C.C{=}CH.CO$$
$$\quad\;|\qquad\;|$$
$$\quad NH.CO.NH$$

With nitrous acid acetoacetic ester yields *iso-nitroso-acetoacetic ester*,

$$CH_3.CO.C(NOH).COOC_2H_5$$

which easily decomposes into alcohol, carbon dioxide, and *iso-nitroso-acetone*.

Tautomerism of Acetoacetic Ester

From its reactions acetoacetic ester may be classed either as the ester of a keto-acid or of an unsaturated hydroxy-crotonic acid. The liquid ester is an equilibrium mixture of the keto and enol forms, the form actually in preponderance depending on various factors.

I. $CH_3—CO—CH_2—COOC_2H_5$ Acetoacetic ester (β- or keto-form)

II. $CH_3—C(OH){=}CH—COOC_2H_5$ *aci*-Acetoacetic ester (α- or enol-form).

Acetoacetic ester represents the oldest and probably the most important example of tautomerism. The problem of its constitution has now been solved, mainly owing to the knowledge gained by the investigations of Knorr [1] and his co-workers in connection with the desmotropy of diaceto-succinic ester. From these researches it was concluded that the velocity of isomerisation of the forms of acetoacetic ester should not be very high, and that a separation might be effected at low temperatures. This conclusion was confirmed by experiment.

At the temperature of a mixture of ether and solid carbon dioxide ($-78°$) it was found that the mutual interconversion of the two forms is practically arrested, and that the individual isomerides could be isolated without any great difficulty.

The Keto-form

Acetyl-acetic ester, $CH_3.CO.CH_2.COOC_2H_5$—generally described by Knorr as the β-ester—may be obtained from the ordinary ester by freezing it out at the temperature of a mixture of ether and solid carbon dioxide. It is difficultly soluble in the majority of organic solvents at this low temperature, and crystallises out from its solutions in alcohol, ether, hexane, ligroin and other solvents which are still liquid at $-78°$. It may thus be separated by filtration. When kept cool in the above mixture, or in liquid air, the keto ester may be preserved for a very long time without noticeable change. Even at the ordinary temperature, in the absence of catalysts, it only returns slowly to the equilibrium mixture during the course of weeks or months. The β-form differs comparatively little from the ordinary (equilibrium) ester, as may be seen from the following data :

	β-Ester	*Equilibrium Mixture.*
Boiling-point (2mm.) .	40° to 41°	39° to 40°
Melting-point . .	−39° (sharply)	−45° to −43° (not sharply)
Refrac. index, n_D^{10} .	1·4225	1·4230 to 1·4235

[1] *Ber.*, 1911, 44, 1138.

While the purity of a keto-form is commonly tested by its failure to give the ferric chloride reaction, the keto-acetoacetic ester at ordinary temperatures shows the same behaviour as the equilibrium mixture, since the addition of the reagent immediately produces from both a large amount of the enolic form. On the other hand, at low temperatures, a decided difference may be observed between the behaviour of the pure keto-ester and that of the ordinary mixture.

Enolic Form

cis-*Hydroxy-crotonic ester*, $CH_3.C(OH):CH.COOC_2H_5$. This form was obtained by Knorr by treating the sodium compound of acetoacetic ester with dry hydrochloric acid gas. It is given the *cis*-configuration

$$\begin{array}{l} H—C—CO_2R \\ \quad\quad\| \\ CH_3—C—OH \end{array}$$

since by virtue of the neighbouring positions of the oxygen groups this should be more acidic than the *trans*-configuration,

$$\begin{array}{l} H—C—CO_2R \\ \quad\quad\| \\ HO—C—CH_3 \end{array}$$

and hence is probably present as such in the salts.

It has been found (K. H. Meyer) that when acetoacetic ester is distilled in a glass flask, the alkali of which acts as a catalyst, the ester is converted into a mixture containing a higher percentage of enol form. Using a quartz flask, however, the distillation proceeds in the absence of catalytic influences, and it is then possible to separate the keto and enolic forms by taking advantage of the difference in boiling-points, little interconversion occurring during the operation. By applying the latter procedure to the richly enolic mixture obtained by distillation in an ordinary flask the enolic form of the ester is readily prepared.[1]

The enolic ester is a colourless oil possessing a powerful and pleasant fruity odour. It does not solidify at the temperature of the ether-carbon dioxide mixture, but in liquid air hardens to a crystalline mass. In small quantities it may be distilled in a high vacuum without much change, boiling at about 33°. The enolic form differs from the keto-form and the equilibrium mixture; it has a much higher refractive index and rapidly gives the colour reaction with ferric chloride, even at low temperatures.

Ketonisation of the Enol-ester.—The enol-form can only be preserved at low temperatures. At room temperature isomerisation is soon noticeable, and even the purest preparation changes back into the equilibrium mixture during the course of ten to fourteen days.

The velocity of isomerisation of the tautomeric forms of acetoacetic ester may be considerably increased by catalytic influences. Contact with soft alkali glass, with a little vapour of hydrochloric acid, tripropylamine or cigarette smoke, or merely handling the liquid in the impure

[1] K. H. Meyer and co-workers, *Ber.*, 1920, **53**, 1410; 1921, **54**, 579.

air of a laboratory, is sufficient in a few seconds or minutes to convert the enolic form into the equilibrium mixture.

The Equilibrium Mixture

Under ordinary conditions the ester is a mixture containing only about 7 per cent. of the enolic form. In the vaporous state it is found that the equilibrium varies with temperature and pressure between the limits of 10 and 30 per cent. enol, so that according to the conditions of experiment the freshly distilled ester may possess the same or a higher enolic content than the normal equilibrium mixture. If the ester is in solution in a volatile solvent the relative proportions of the isomerides present may be determined by cooling to $-78°$, removing the solvent *in vacuo*, and estimating the composition of the residual mixture by measuring the refractive index. A 30 per cent. solution in ether is thus found to contain 11 per cent. of the enol-form. The proportion of enolic form in the mixture may also be estimated by rapid titration with a cold solution of bromine in methyl alcohol,[1] when addition to the double bond occurs quantitatively.

Laevulinic acid, *β-acetyl-propionic acid,* $CH_3.CO.CH_2.CH_2.COOH$, is the simplest γ-ketonic acid. It is formed when a hexose, especially laevulose, is boiled with dilute sulphuric or hydrochloric acid. Laevulinic acid is prepared by heating starch or cane sugar with hydrochloric acid. It may be obtained synthetically by combining sodium acetoacetic ester with chloro-acetic ester and submitting the resulting product to ketonic hydrolysis :

$$CH_3.CO.\underset{\displaystyle COOC_2H_5}{\underset{|}{CH}}.CH_2.COOC_2H_5 \longrightarrow CH_3.CO.CH_2.CH_2.COOH + CO_2 + 2C_2H_5OH$$

The acid is crystalline, melts at 32·5° and boils with slight decomposition at 250°. It is very readily soluble in water, alcohol, and ether, shows the characteristic reactions of ketones (formation of oxime, hydrazone, etc.), and on electrolysis of its potassium salt yields 2 : 7-octanedione.

$$\begin{matrix} CH_3.CO.CH_2.CH_2 \\ CH_3.CO.CH_2.CH_2 \end{matrix}\!\!\begin{matrix} \vdots COO \vdots \\ \vdots COO \vdots \end{matrix}\!\!\begin{matrix} -K \\ -K \end{matrix} + 2H_2O = \begin{matrix} CH_3.CO.CH_2.CH_2 \\ | \\ CH_3.CO.CH_2.CH_2 \end{matrix} + 2KHCO_3 + H_2$$

When heated for a considerable time at their boiling-points, γ-ketonic acids lose water and pass into unsaturated lactones. Like γ-diketones, they may also be used in the preparation of pyrrole derivatives.

[1] K. H. Meyer, *Ann.*, 1911, **380**, 202.

XV

Polybasic Acids

I.—SATURATED DIBASIC ACIDS, $C_nH_{2n}(COOH)_2$

Formation.—Dibasic acids are found to some extent in nature, and may be obtained artificially by methods similar to those used for the monobasic acids (see p. 193). Chief among these are the oxidation of the corresponding glycols, aldehydes, hydroxy-acids or aldehydic acids, the hydrolysis of dicyanides, *e.g.* $CN.CH_2.CH_2.CN$, or of cyano-substituted monocarboxylic acids, *e.g.* $CN.CH_2.COOH$, and the acid hydrolysis of substituted acetoacetic esters (see p. 264), *e.g.*,

$$\underset{\text{Sodium acetoacetic ester}}{CH_3.CO.CHNa.COOEt} \xrightarrow{Cl.CH_2.COOEt} CH_3.CO.CH\begin{matrix}COOEt\\CH_2.COOEt\end{matrix} \xrightarrow[\text{hydrolysis}]{\text{Acid}} \underset{\text{Succinic acid.}}{\begin{matrix}CH_2.COOH\\|\\CH_2.COOH\end{matrix}}$$

Aceto-succinic ester.

Properties.—The dibasic acids are solid crystalline compounds of strong acidic character. In most cases they dissolve readily in water, the solubility of an acid containing an uneven number of carbon atoms being greater than that of the next higher acid with an even number. A similar regularity is found in the melting-points, an acid with an even number of carbon atoms melting higher than the following member containing an odd number.

A point to be noted is the varying behaviour of the dibasic acids under the influence of heat. In some cases anhydrides are formed, whilst in others carbon dioxide is eliminated.

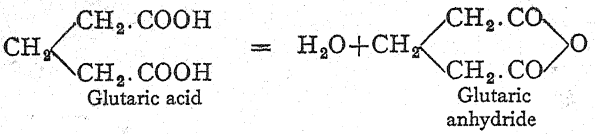
Oxalic acid, HOOC.COOH, and all those homologues in which, as in the case of malonic acid, $CH_2(COOH)_2$, the two carboxyl groups are attached to the same carbon atom, decompose on heating to give carbon dioxide and a monobasic acid.

$$\underset{\text{Oxalic acid}}{HO_2C.CO_2H} = CO_2 + \underset{\text{Formic acid}}{H.CO_2H}$$

$$\underset{\text{Malonic acid}}{HO_2C.CH_2.CO_2H} = CO_2 + \underset{\text{Acetic acid}}{CH_3.CO_2H}$$

On the other hand, dibasic acids in which the carboxyl groups are linked to different carbon atoms—as in succinic and glutaric acids—generally lose a molecule of water under the influence of heat and yield an intramolecular anhydride, *e.g.*,

$$\underset{\text{Succinic acid}}{\begin{matrix}CH_2—COOH\\|\\CH_2—COOH\end{matrix}} = H_2O + \underset{\text{Succinic anhydride}}{\begin{matrix}CH_2.CO\\|\\CH_2.CO\end{matrix}}\!\!>O$$



The tendency towards anhydride formation of this character varies very largely with different acids. It is particularly marked in cases where by elimination of water a five- or six-membered ring may be formed, and it must be assumed that this type of reaction depends on the relative positions in space of the two carboxyl groups.

Those dicarboxylic acids in which the two acid groups are separated by more than four carbon atoms either volatilise unchanged on heating or undergo radical decomposition accompanied by charring.

Nomenclature and Isomerism.—The majority of the acids take their names from their origin or method of preparation. According to the " Geneva nomenclature " the names are derived from those of the corresponding hydrocarbons, in the same manner as in the case of monobasic acids.

Among the higher members a number of structural isomerides are possible, according to the relative positions of the two carboxyl groups in the carbon chain.

Of the very large number of compounds belonging to this class, only the more important will be described here.

Oxalic acid, *ethane diacid,* HOOC.COOH, occurs very extensively in the vegetable kingdom, particularly as the potassium salts in plants of the *oxalis* and *rumex* families. In the animal organism it is found as the calcium salt. It is formed during the oxidation of many organic compounds, and is prepared industrially from cellulose by fusing sawdust with sodium or potassium hydroxide in iron pans at about 240°.

The sawdust, preferably obtained from a soft wood, is uniformly impregnated with the alkali, two parts of the latter being used to one part of wood. After fusing the mixture till all the cellulose has disappeared, the melt is extracted with hot water, and the sparingly soluble sodium oxalate allowed to crystallise out. By the addition of milk of lime the sodium salt is converted into calcium oxalate and sodium hydroxide, from the former of which free oxalic acid is obtained by treatment with sulphuric acid.

$$Na_2C_2O_4+Ca(OH)_2 = CaC_2O_4+2NaOH\,;\ CaC_2O_4+H_2SO_4 = CaSO_4+H_2C_2O_4$$

The sodium hydroxide contained in the mother liquors is recovered and utilised for the oxidation of further quantities of cellulose.

Additional methods of preparing oxalic acid are by the rapid heating of sodium formate,

$$2HCOONa = H_2+C_2O_4Na_2$$

and by the direct combination of carbon dioxide with sodium at 360°.

$$2CO_2+2Na = Na_2C_2O_4$$

Properties.—Oxalic acid crystallises in monoclinic prisms containing 2 mols. water of crystallisation. The anhydrous acid melts at 190° and the hydrated form at 101°. Oxalic acid is poisonous. When carefully heated to 150° it sublimes, but on rapid heating it decomposes partly

into carbon monoxide and formic acid (see p. 194), and partly into carbon dioxide, carbon monoxide and water. These last products are obtained exclusively on warming oxalic acid with concentrated sulphuric acid or acetic anhydride.

$$H_2C_2O_4 = CO_2 + CO + H_2O$$

The addition of very small quantities of water to the sulphuric acid results in a marked diminution in the velocity of decomposition.

When treated with potassium permanganate in acid solution, oxalic acid is readily oxidised to carbon dioxide and water, a reaction frequently utilised in volumetric analysis.

$$H_2C_2O_4 + O = 2CO_2 + H_2O$$

By the electrolytic reduction of oxalic acid in sulphuric acid solution, using a lead or mercury cathode, Tafel and Friedrichs obtained good yields of glyoxalic acid.[1]

Oxalic acid and its antimony salt are used as mordants in the printing and dyeing industries. It is also employed for whitening leather, removing ink and rust stains, bleaching and cleaning straw and stearine goods, in the manufacture of inks and the preparation of certain coal-tar dyes. Ferrous oxalate is used as a photographic developer, and potassium ferric oxalate, $K_3Fe(C_2O_4)_3$, in platinum printing.

Salts of Oxalic Acid

Only the alkali salts of oxalic acid are soluble in water. In addition to the neutral and acid salts, *tetroxalates* are known, formed by the combination of a molecule of the acid salt with a molecule of oxalic acid, *e.g.* the *potassium tetroxalate* of commerce, $KHC_2O_4,H_2C_2O_4,2H_2O$. The *calcium salt*, CaC_2O_4,H_2O, is insoluble in water or acetic acid, and is used for the detection and quantitative estimation of both calcium and oxalic acid. The oxalates of silver and mercury, on being heated, decompose explosively into the metal and carbon dioxide. Among the above-mentioned oxalates of iron, potassium ferric oxalate, $K_3Fe(C_2O_4)_3$, is of special interest. In sunlight, an aqueous solution of this salt is rapidly reduced to potassium ferrous oxalate,

$$2K_3Fe(C_2O_4)_3 = 2K_2Fe(C_2O_4)_2 + K_2C_2O_4 + 2CO_2$$

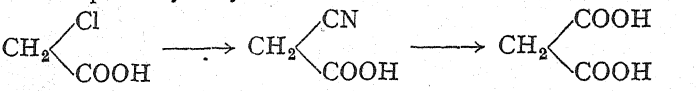
and this property is utilised in the following manner in platinum printing. The photographic negative is laid on paper which has been prepared with potassium ferric oxalate, and exposed to light. Where the light penetrates, reduction takes place. On now bringing the paper into a solution of platinum chloride, the ferrous oxalate present reduces the solution, depositing metallic platinum on those parts affected by the light.

Esters and Other Derivatives of Oxalic Acid

Dimethyl oxalate, $CH_3OOC.COOCH_3$, m.p. 51°, b.p. 162°, is useful in the preparation of pure methyl alcohol. The solid ester obtained from the crude alcohol is readily purified by crystallisation, and may then be hydrolysed to yield oxalic acid and the pure alcohol. *Diethyl oxalate*, $C_2H_5OOC.COOC_2H_5$, b.p. 186°, condenses with acetic ester to give oxalo-acetic ester (p. 263). *Oxamic acid*,[2] $HOOC.CONH_2$, is the monoamide of oxalic acid, and is formed by heating ammonium hydrogen oxalate. It is a powder, melting with decomposition at 210°. *Oxamide*, $NH_2.OC.CO.NH_2$, the diamide of oxalic acid, is formed in a variety of ways, such as by the action of ammonia on ethyl oxalate. It is a white powder which is almost insoluble in water.

[1] *Ber.*, 1904, **37**, 3189. [2] The mono-amides of dibasic acids are known generally as -amic acids.

Malonic acid, $CH_2(COOH)_2$, occurs in beetroot. It is obtained from chloroacetic acid by heating it with potassium cyanide to give cyanoacetic acid, and subsequent hydrolysis.



Malonic acid crystallises in large leaves or plates, m.p. 132°. When heated it decomposes into carbon dioxide and acetic acid. Its esters are of great value in the synthesis of organic compounds.

Diethyl malonate, $CH_2(COOC_2H_5)_2$, is conveniently prepared from cyanoacetic acid by the action of alcohol and sulphuric acid, the malonic acid first produced being converted into the ester.[1] It is a colourless liquid, b.p. 198°, having a faintly aromatic smell. With phosphorus pentoxide it yields the double ketene O:C:C:C:O, known as *carbon suboxide*.[2] The latter is a liquid of powerful odour boiling at 7°.

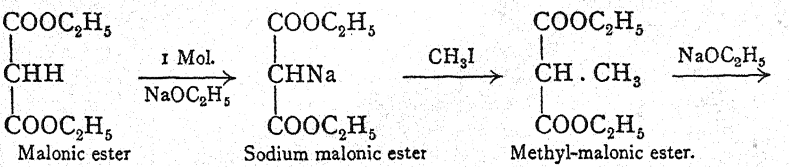
$$\underset{\text{Ethyl malonate}}{CH_2(CO_2C_2H_5)_2} = \underset{\text{Ethylene}}{2C_2H_4} + 2H_2O + \underset{\text{Carbon suboxide.}}{OC:C:CO}$$

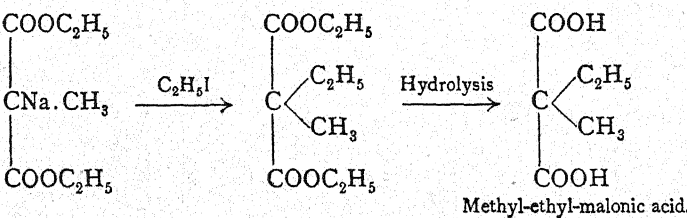
Malonic acid itself also decomposes into carbon suboxide on heating with phosphorus pentoxide, and is recommended by Diels as the best starting material for the preparation of this compound.

Esters of malonic acid resemble acetoacetic ester in that—owing to the influence of the neighbouring carbonyl groups—the two hydrogen atoms of the methylene group may be replaced successively by sodium. The metal can then be exchanged for other groups by bringing the sodium compound into reaction with organic halogen compounds (*e.g.* alkyl and acyl halides).

In the "malonic ester syntheses" we have a valuable method for the preparation of dibasic acids of the general types $CHX(COOH)_2$ *and* $CXY(COOH)_2$.

The following scheme represents a typical synthesis of this kind.





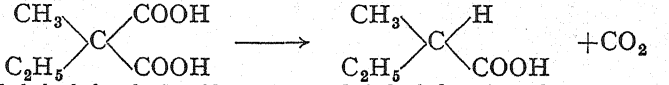
For further information reference should be made to the similar case of acetoacetic ester, which has been dealt with in detail.

[1] W. A. Noyes, *J. Am. C. S.*, 1896, **18**, 1105. [2] Diels and Wolf, *Ber.*, 1906, **39**, 689; 1907, **40**, 355; 1926, **59**, 2555. M. J. Edwards and J. M. Williams, *J. C. S.*, 1927, 855.

It has already been mentioned that those dicarboxylic acids in which the two acid groups are separated by a single carbon atom readily lose carbon dioxide when heated, and pass into monobasic acids.

From the dibasic acids synthesised by the above method we can therefore obtain by the action of heat substituted acetic acids of the type $CH_2X.COOH$ *and* $CH(XY).COOH$.

For example,



Methyl-ethyl-malonic acid — Methyl-ethyl-acetic acid.

These substituted acetic acids can also be obtained by the acid hydrolysis of acetoacetic ester derivatives, as described on p. 264. In this case, however, a certain amount of ketonic hydrolysis usually occurs at the same time, reducing the yield of acid. On the other hand, in malonic ester syntheses the substituted malonic acids decompose in one direction only, and it is therefore more expedient to use this method for the preparation of the homologous fatty acids.

Like acetoacetic ester, malonic ester may also react in the *enolic form*, $H_5C_2OOC.CH : C(OH).OC_2H_5$, although the proportion of this present in the ordinary ester appears to be extremely small. Probably the sodium derivative is of enolic type.

Electrosynthesis by Means of Malonic Ester

Syntheses effected by electrolytic means in organic chemistry are not very numerous, but the method has been applied with great success to salts of the monoesters of dibasic acids, and of malonic acid in particular.

Brown and Walker [1] found that on electrolysing the aqueous solution of an alkali salt of a monoester of a dicarboxylic acid (*e.g.* potassium ethyl malonate) the free carboxyl group was eliminated as carbon dioxide, and two of the residues thus produced united together, as in the Kolbe synthesis of ethane (p. 110), to form the diester of a higher dicarboxylic acid. In this manner the more complex dibasic acids were prepared synthetically from lower homologues : *e.g.* succinic ester was obtained from potassium ethyl malonate :

$$2C_2H_5O.OC.CH_2.COOK \longrightarrow C_2H_5OOC.CH_2.CH_2.COOC_2H_5$$

Potassium ethyl malonate — Diethyl succinate

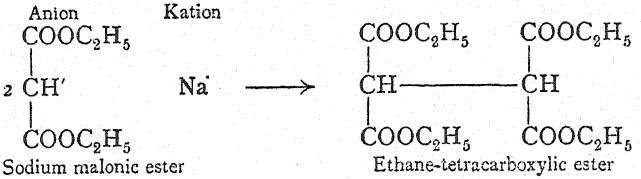
By starting from the ethyl potassium salt of a substituted malonic acid the reaction gives a substituted succinic ester, *e.g.*,

$$C_2H_5OOC.CH(CH_3).COOK \longrightarrow C_2H_5OOC.CH(CH_3).CH(CH_3).COOC_2H_5$$

If both carboxyl groups in a dibasic acid are esterified, the diester may still function as an acid on electrolysis, provided that a methylene group of pronounced acidic character is present. The dialkyl esters of sodium malonic acid, in particular, resemble carboxylic acids in their behaviour on electrolysis, the two anions uniting together to form *ethane-*

[1] *Ann.*, 1891, **261**, 107 ; 1893, **274**, 41.

tetracarboxylic ester. The compound so obtained is thus the same as that formed by removing the sodium with iodine.



Sodium malonic ester — Ethane-tetracarboxylic ester

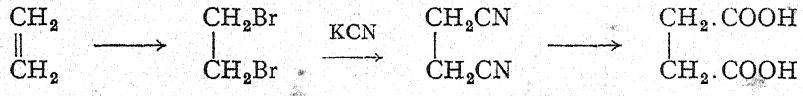
It may also be mentioned that when a salt of a monoester of a dibasic acid is mixed with a salt of a fatty acid and submitted to electrolysis, an ester of a higher monobasic acid is produced. In this way ethyl butyrate is obtained from a mixture of potassium acetate and ethyl potassium succinate.

$$CH_3.COOK + KOOC.CH_2.CH_2.COOC_2H_5 \longrightarrow CH_3.CH_2.CH_2.COOC_2H_5$$

Methyl-malonic acid, $CH_3.CH(COOH)_2$, m.p. 130°, is prepared from sodio-malonic ester and methyl iodide, or by the hydrolysis of cyanopropionic acid, $CH_3.CH(CN).COOH$. It is isomeric with succinic acid and is therefore sometimes termed isosuccinic acid or ethylidene succinic acid. At 150° it decomposes into propionic acid and CO_2.

Succinic acid, *ethylene succinic acid, butane diacid,* $HOOC.CH_2.CH_2.COOH$, occurs in amber, in a few resins and brown coal, in many plants and in the animal organism. It is formed in small amounts during the alcoholic fermentation of sugar, and is prepared by distillation of amber or from calcium malate by fermentation. It may be synthesised by the following reactions :

1. From ethylene cyanide by hydrolysis,



2. From malonic acid by electrolytic methods (see p. 273) ; also by the " malonic ester synthesis,"

$$(COOC_2H_5)_2CHNa + Cl.CH_2.COOC_2H_5 \longrightarrow (COOC_2H_5)_2CH.CH_2.COOC_2H_5$$

Sodium malonic ester — Chloroacetic ester — Ethane-tricarboxylic ester

$$\xrightarrow{\text{hydrolysis}} (COOH)_2CH.CH_2.COOH$$

$$\xrightarrow{\text{heat}} HOOC.CH_2.CH_2.COOH + CO_2$$

It is readily seen that alkyl-substituted succinic acids can also be obtained by this reaction, by combining alkyl-substituted sodium malonic esters, $NaRC(COOC_2H_5)_2$, with alkyl-substituted chloroacetic esters of the general formula

$$Cl.CHR'.COOC_2H_5 \text{ and } ClCR'R''.COOC_2H_5.$$

An additional method of passing from the malonic acid to the succinic acid series consists in removing sodium from sodium malonic esters by means of iodine, hydrolysing the ethane tetracarboxylic ester so formed

(p. 274), and then splitting off carbon dioxide from the free tetracarboxylic acid at a higher temperature.

Among other reactions leading to the formation of succinic acid may be mentioned the reduction of its hydroxy derivatives malic and tartaric acids, and also of fumaric and maleic acids.

Succinic acid crystallises in monoclinic prisms, m.p. 185°, and boils at 235° with partial conversion into the anhydride. At the ordinary temperature it is soluble in twenty parts of water. The potassium salt yields ethylene on electrolysis.

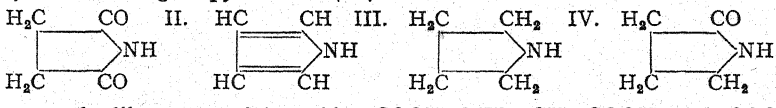
Brown and Walker (p. 273) found that the main product of the electrolysis of ethyl potassium succinate was the diethyl ester of adipic acid :

$$2COOC_2H_5.(CH_2)_2.COOK \longrightarrow COOC_2H_5.(CH_2)_4.COOC_2H_5$$

Among other important *derivatives of succinic acid*, the hydroxy compounds, **malic acid** and **tartaric acid**, and the **ester of diaceto-succinic acid**, are described in detail later. Of the *succinates*, the alkali salts are readily soluble in water, and those of other metals insoluble or only sparingly soluble.

Esters : **Methyl succinate**, $C_2H_4(COOCH_3)_2$, is a solid at ordinary temperatures and melts at 19° ; the **ethyl ester** boils at 218°, and undergoes a remarkable condensation under the influence of sodium, to give a cyclic compound *succinylo-succinic ester* (p. 468).

Succinimide (I) is produced by heating ammonium succinate, and is a solid, m.p. 126° and b.p. 228°. It is acidic in character, the hydrogen of the NH— group being replaceable by metals. When distilled with zinc dust it is converted into *pyrrole* (II), and when reduced with sodium in boiling alcoholic solution it yields *pyrrolidine* (III). Electrolytic reduction gives *pyrrolidone* (IV).



Mono- and **dibromo-succinic acids**, $COOH.CHBr.CH_2.COOH$ and $COOH.CHBr.CHBr.COOH$, are readily obtained by the action of bromine on succinic acid, and are used in the synthesis of the hydroxy acids.

Methyl-succinic acid, pyro-tartaric acid, $CH_3.CH(COOH).CH_2.COOH$, m.p. 112°, is formed (together with pyruvic acid) by the dry distillation of tartaric acid, and also by the acetoacetic ester synthesis. It contains an asymmetric carbon atom and can be resolved into its optically active components by means of strychnine.

Symmetrical dialkyl-succinic acids, such as dimethyl-succinic acid, $COOH.CH(CH_3).CH(CH_3).COOH$, are known in two forms corresponding to the meso and racemic compounds. Up to the present all attempts to resolve one of these into its optically active components have failed. In the case of the *sym.* diphenyl-succinic acids, however, the existence of this type of isomerism has been definitely established,[1] the *r*-acid being identified by its resolution into *d*- and *l*-forms.

Trimethyl-succinic acid, $COOH.CH(CH_3).C(CH_3)_2.COOH$, is formed as its anhydride by distillation of camphoronic acid, and is therefore of importance in connection with the constitution of camphor.

[1] H. Wren, *J. C. S.*, 1915, **108**, 444.

Glutaric acid, *pentane diacid*, $COOH.CH_2.CH_2.CH_2.COOH$, m.p. 97°, may be prepared from trimethylene bromide *via* the cyanide $CN.CH_2.CH_2.CH_2.CN$, or from *methylene dimalonic acid* (from sodiomalonic ester and methylene iodide) by loss of CO_2.

$$(CO_2C_2H_5)_2CHNa + I.CH_2.I + NaCH(CO_2C_2H_5)_2 \longrightarrow (CO_2C_2H_5)_2CH{-}CH_2{-}CH(CO_2C_2H_5)_2$$

Methylene dimalonic ester

$$\longrightarrow (CO_2H)_2CH{-}CH_2{-}CH(CO_2H)_2 \longrightarrow CO_2H.CH_2{-}CH_2{-}CH_2.CO_2H$$

Methylene dimalonic acid — Glutaric acid.

The main interest of the following higher dicarboxylic acids lies in the *cyclic ketones* formed by heating their calcium salts.

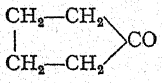
Adipic acid, $COOH.(CH_2)_4.COOH$, m.p. 153°, was first obtained by the oxidation of fat (*adeps*, fat) by means of nitric acid, and is best prepared by oxidising cyclohexanol with alkaline potassium permanganate. The barium salt on dry distillation yields *keto-pentamethylene* or *cyclo-pentanone* (I), together with barium carbonate.

Normal pimelic acid, $COOH.(CH_2)_5.COOH$, is formed synthetically from sodium malonic ester and trimethylene bromide. It melts at 103°, and on distillation of the calcium salt yields *keto-hexamethylene* or *cyclo-hexanone* (II). It is also obtained as a degradation product of the alkaloids atropine and cocaine, thus showing that these contain the carbon chain of *n*-pimelic acid in the form of a seven-membered ring.

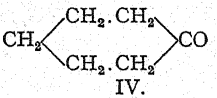
Suberic acid, $COOH.(CH_2)_6.COOH$, m.p. 140°, occurs in the skin of the toad, and is prepared by the oxidation of cork (*suber*, cork). Brown and Walker showed that the ester of this acid is formed by the electrolysis of ethyl potassium glutarate. It may also be synthesised by the action of magnesium and carbon dioxide on trimethylene bromide in dry ethereal solution. When the calcium salt is distilled, *keto-heptamethylene*, *cyclo-heptanone* or *suberone* (III) is obtained.

Azelaic acid, $COOH.(CH_2)_7.COOH$, m.p. 107°, is formed by the oxidation of oleic acid with nitric acid, or synthetically from sodium acetoacetic ester and pentamethylene bromide. On distillation with lime it gives *cyclo-octanone* (IV) but much better yields are obtained by use of the thorium salt.

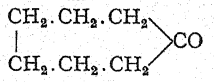
I.



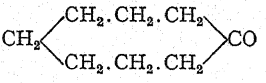
II.



III.



IV.



Sebacic acid, $COOH.(CH_2)_8.COOH$, m.p. 133°, is obtained when stearic acid, spermaceti or castor oil is oxidised with nitric acid.

II.—UNSATURATED DIBASIC ACIDS

Those dibasic acids in which ethylene linkages are present may be regarded as dicarboxylic derivatives of the olefins, a classification which is in agreement with their chemical behaviour. As acids they form derivatives similar to those of the saturated dibasic acids described above, and as olefins they possess additive properties, uniting with two atoms of hydrogen or halogen, or with one molecule of hydrogen halide. The most important representatives in this group are *fumaric* and *maleic*

acids, $C_4H_4O_4$, both of which have been shown to be symmetrical dicarboxylic derivatives of ethylene. These two acids form one of the best known and most completely investigated cases of geometrical isomerism among symmetrically substituted ethylene derivatives. This type of isomerism has already been discussed in the theoretical section of this book (see p. 48).

Fumaric acid, *trans-butene diacid*, $\begin{matrix} H—C—COOH \\ \| \\ HOOC—C—H \end{matrix}$, occurs in many plants, such as Iceland moss and *Fumaria officinalis*. It is formed as the chief product of reaction when malic acid is heated for a considerable time at 140° to 150°,

$$\underset{\text{Malic acid}}{COOH.\dot{C}H—\dot{C}H.COOH} = \underset{\text{Fumaric acid}}{COOH.CH:CH.COOH} + H_2O$$
$$\quad\quad\quad

Interconversion of Fumaric and Maleic Acids

It is a characteristic of geometrical isomerides that under certain conditions they are readily transformed into one another.

Thus fumaric acid is converted into maleic anhydride on being heated, or by the action of phosphorus pentachloride, oxychloride or pentoxide.

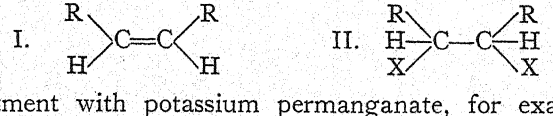
Maleic acid, on the other hand, passes without difficulty into fumaric acid if heated alone at 140°, in aqueous solution at 200° to 220°, or in benzene solution at 130°. The same change may also be effected under the influence of bromine (in sunlight), or of hydrogen halides, sulphurous acid, nitrous acid or hydrogen sulphide. A trace of piperidine converts methyl maleate in a few seconds into a crystalline mass of methyl fumarate.[1] Free maleic acid gives a quantitative yield of fumaric acid when boiled with aqueous mercuric chloride and a trace of potassium persulphate [2]; the same reagents bring about the conversion of citraconic acid (see below) into itaconic acid,[3] and of oleic into elaidic acid.

Determination of the Configuration of Geometrical Isomers in the Ethylene Series

The ease with which maleic acid forms an anhydride, coupled with the fact that fumaric acid yields none, is sufficient to characterise the former without doubt as the *cis*-modification, since in this case the carboxyl groups are in the neighbouring position necessary for anhydride formation. In this property we have a general means of determining the configuration of unsaturated dibasic acids of the type $COOH.CR{=}CR.COOH$. As maleic acid is the simplest *cis*-acid, compounds of similar configuration are sometimes known as " maleinoid forms," and those corresponding to fumaric acid as " fumaroid forms."

Among numerous examples of this kind may be mentioned the next higher homologues of fumaric and maleic acid, both of the structural formula $COOH.C(CH_3){=}CH.COOH$. Of these, the maleinoid form is called *citraconic acid* and the fumaroid form *mesaconic acid*.

Another but less certain method of determining the configuration is to convert the isomerides into symmetrical derivatives of ethane, containing two asymmetric carbon atoms. The addition of two similar atoms or groups (X) to the *cis*-form of a symmetrically constituted ethylene compound (I) would be expected to lead to the formation of an inactive, internally-compensated (meso-)compound (II). On the other hand, the *trans*-form would be expected to give the corresponding racemic compound.



On treatment with potassium permanganate, for example, maleic acid takes up two hydroxyl groups to form meso-tartaric acid, whereas fumaric acid is oxidised to racemic acid.

[1] Clemo and Graham, *J. C. S.*, 1930, 213. [2] H. Wieland and W. Zilg, *Ann.*, 1937, 530, 273
[3] The double bond is here displaced into the side chain ($CH_2{=}$).

This method, however, must be applied with caution. It has been shown by McKenzie that the dibromo-succinic acid formed by addition of bromine to maleic acid is the racemic compound,[1] and not the meso-compound.

Among physical methods, one of the most valuable means of distinguishing between the *cis* and *trans* forms of compounds containing polar groups is by a comparison of their dipole moments (see p. 82).

An interesting unsaturated dicarboxylic acid is **glutaconic acid,** $HOOC.CH:CH.CH_2.COOH$. Owing to the mobility of the hydrogen attached to the carbon chain, alkyl derivatives of this acid exhibit a special type of isomerism. This subject has been extensively studied by Thorpe and his co-workers. For further details see p. 66.

Dibasic acids are also known containing triple bonds in the molecule. The simplest of these is **acetylene dicarboxylic acid,** $COOH.C{\equiv}C.COOH$, which crystallises with two molecules of water, and is prepared from dibromo-succinic acid by treatment with alcoholic potash. When the potassium hydrogen salt of this acid is warmed with water it decomposes into carbon dioxide and potassium propiolate, $CH:C.COOK$ (see p. 206). The cuprous compound of potassium propiolate is oxidised by potassium ferricyanide to give copper oxide, the two propiolic residues uniting to form the potassium salt of **diacetylene dicarboxylic acid :**

$$2KOOC.C:C.Cu+2O = KOOC.C:C.C:C.COOK+2CuO$$

By a repetition of the above process **tetra-acetylene dicarboxylic acid** is obtained,

$$2KOOC.C:C.C:C.Cu \longrightarrow KOOC.C:C.C:C.C:C.C:C.COOK$$

These compounds are very unstable, and as the chain increases in length show an increasing tendency to explode.

It is to be noted that the acetylene carboxylic acids are comparatively strong acids, as may be seen from their dissociation constants. A triple bond, and to a less extent a double bond, therefore leads to an increase of acidic character.

III.—ACIDS OF HIGHER BASICITY

With regard to the constitution of acids of higher basicity, it is to be remembered that, as in the case of certain other poly-substituted compounds already discussed, the presence of more than one carboxyl group attached to the same carbon atom leads to instability. No compound is known containing more than two carboxyl groups in this state of combination.

Tricarballylic acid, *sym. propane tricarboxylic acid,*

$$CH_2(CO_2H).CH(CO_2H).CH_2(CO_2H)$$

occurs in unripe beetroots. It may be formed synthetically by various reactions, *e.g.* from allyl tribromide, by conversion into the tricyanide and subsequent hydrolysis,

$$\underset{\text{Allyl tribromide}}{CH_2Br{-}CHBr{-}CH_2Br} \longrightarrow \underset{\text{Allyl tricyanide.}}{CH_2(CN){-}CH(CN){-}CH_2(CN)} \longrightarrow CH_2(CO_2H){-}CH(CO_2H){-}CH_2(CO_2H)$$

[1] *J. C. S.*, 1912, **101**, 1196.

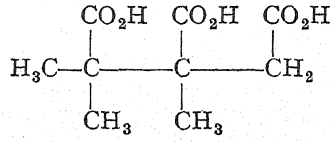
also by the condensation of sodium malonic ester and monochloro-succinic ester. The ester so formed,

$$(C_2H_5OOC)_2CH.CH(COOC_2H_5).CH_2.COOC_2H_5$$

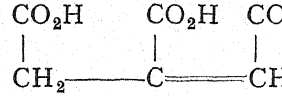
is hydrolysed and the acid heated to drive off carbon dioxide. Tricarballylic acid melts at 162° to 164° and is readily soluble in water.

A monohydroxy derivative of this acid is citric acid, which is dealt with later.

Camphoronic acid, *αα'β-trimethyl-tricarballylic acid*, m.p. 135°, is



formed by the oxidation of camphor. The determination of its constitution by Perkin and Thorpe [1] provided valuable evidence in connection with the structure of camphor.

Aconitic acid,  , is an example of an unsaturated tribasic acid. It occurs in various plants, *e.g.* in *Aconitum napellus*, in beetroot and in sugar cane, and is formed by removing the elements of water from citric acid. On reduction it takes up two atoms of hydrogen and is converted into tricarballylic acid.

Acids of higher basicity than these do not appear to occur in nature, but can be synthesised from acetoacetic ester or malonic ester. In this way acids have been obtained having as many as fourteen carboxyl groups in the molecule.

XVI

Polybasic Acids containing Hydroxy, Amino, Aldehydic and Ketonic Groups

In chemical behaviour and general methods of preparation these compounds resemble the corresponding derivatives of the monobasic acids previously described.

Dibasic Hydroxy Acids

The simplest compounds of this class are derived from malonic acid.

Tartronic acid, *hydroxy-malonic acid*, COOH.CHOH.COOH, is formed from chloro- or bromo-malonic acid by replacing halogen with hydroxyl, or from glycerol by oxidation with permanganate. It crystallises in large, colourless prisms which melt with evolution of carbon dioxide at 184°. As will be seen later, *mesoxalic acid* may be regarded as *dihydroxy-malonic acid.*

[1] *J. C. S.*, 1897, 1169.

Of far greater importance than the hydroxy derivatives of malonic acid are those of succinic acid, namely malic and tartaric acids.

Malic acid, *hydroxy-succinic acid, butanol diacid,* $\begin{matrix} HO.CH.COOH \\ | \\ CH_2.COOH, \end{matrix}$ is widely distributed in the vegetable kingdom, occurring for example in sour apples, grapes and the berries of the mountain ash. It is best obtained from the last source. As may be seen from the above formula it contains an asymmetric carbon atom, and may therefore exist in *d*-, *l*- and *r*-forms (see p. 33). The acid obtained from the above natural sources is the *laevorotatory* form, which is frequently described as *ordinary malic acid.*

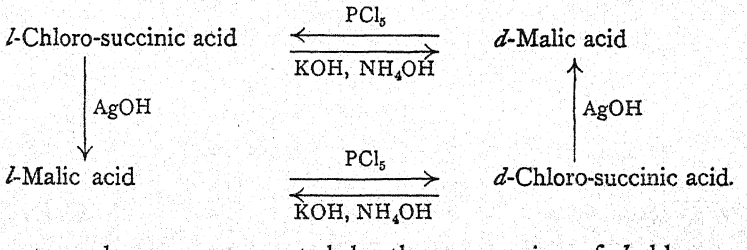
r-*Malic acid* may be obtained in various ways, such as by reducing racemic acid with hydriodic acid, and by heating fumaric or maleic acid to 100° with aqueous sodium hydroxide.

d-*Malic acid* is obtained by resolving the racemic form by means of the cinchonine salt, or by reducing ordinary (dextro-)tartaric acid with hydriodic acid. As will be seen below, the two active malic acids can be converted into one another through the chloro-succinic acids (Walden inversion).

l-Malic acid forms deliquescent needles, readily soluble in water and alcohol, but difficultly soluble in ether. It melts at 100°, and on further heating yields, according to conditions, either fumaric acid or maleic anhydride. Reduction converts it into succinic acid. When heated with strong sulphuric acid it yields *coumalinic acid*; with sulphuric acid and phenols it gives *coumarins* (see index).

Three of the four groups linked to the asymmetric carbon atom in malic acid are readily attacked by chemical reagents. Many derivatives are therefore known which may also exhibit optical activity, provided that the asymmetry of the molecule has not been destroyed at any time during their formation. The rotation of the derivative is usually in the same direction as that of the original acid, but in some cases the sign of rotation is reversed, and in others a racemic compound is formed.

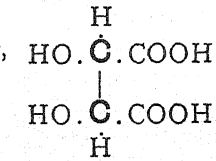
A peculiar phenomenon was discovered by P. Walden during the interconversion of malic acids and chloro-succinic acids. The observed changes in optical activity may be summarised as follows :—



The two changes represented by the conversion of *l*-chlorosuccinic acid into *l*-malic acid on the one hand and into *d*-malic acid on the other (by use of AgOH and KOH respectively) cannot both be considered

as normal reactions. If one of them is a simple replacement of Cl by OH, the other must be a replacement accompanied by molecular rearrangement resulting in the production of the mirror-image of the expected structure. A change of the latter type, which makes it possible to pass from one optical isomeride to the other, is termed an *optical inversion* or *Walden inversion*, and usually occurs with some degree of racemisation. Many other such reactions have been studied,[1] but the cause of the inversion still awaits explanation.[2]

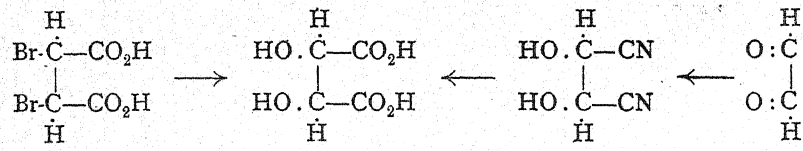
Tartaric acids, *dihydroxy-succinic acids,* *hydroxy-malic acids, butane-diol diacids.*



Special interest attaches to the tartaric acids, because the investigation of these compounds by Pasteur led to the first real advances in our knowledge of optical activity. Even to-day these acids are the best known and most completely investigated examples of compounds containing two similar asymmetric carbon atoms.

As explained in the introductory section of this book (p. 34), there are in agreement with theory four stereoisomeric tartaric acids, distinguished as *dextro-tartaric acid, laevo-tartaric acid, racemic acid and meso-tartaric acid* respectively. The following description deals in the main with their chemical properties, and for a discussion of their stereochemical differences reference should be made to the general section.

The structural formula quoted above has been verified experimentally by the synthesis of the inactive acids, *e.g.* from the silver salt of dibromosuccinic acid by boiling with water, or from glyoxal by addition of hydrogen cyanide and hydrolysis of the resulting nitrile :



1. Dextro-tartaric acid, *d*-tartaric acid, is the common form of tartaric acid. It is found in different varieties of fruit, particularly in grapes, as the potassium hydrogen salt, $KHC_4H_4O_6$. The crude salt, known as *argol* or *tartar*, is an important by-product of the wine industry. Owing to its insolubility in dilute alcohol, it separates during fermentation in hard brown crusts in the vats and storage tubs. It serves as the raw material for the *technical preparation of tartaric acid*, which is carried out as follows :

Crude tartar is neutralised by boiling with water and chalk, when half of the original

[1] See *Optische Umkehrerscheinungen* (*Waldensche Umkehrung*), published by Vieweg and Son, Brunswick, 1920; also Cohen, *Organic Chemistry*, Vol. II. (Arnold). [2] A suggestion based on the polarity of the reacting complexes has been advanced by Kenyon and Phillips, *Trans. Farad. Soc.*, 1930, 451.

tartrate is converted into the sparingly soluble calcium salt, the other half remaining in solution as the di-potassium salt.

$$2KHC_4H_4O_6+CaCO_3 = CaC_4H_4O_6+K_2C_4H_4O_6+CO_2+H_2O$$

By the addition of calcium chloride, the dissolved salt is also transformed into the calcium salt. The precipitated calcium tartrate is then separated and decomposed with dilute sulphuric acid. The solution is filtered off from calcium sulphate and evaporated under reduced pressure in a vessel lined with lead, when crude tartaric acid crystallises out. It is purified by decolorisation with animal charcoal and re-crystallisation.

d-Tartaric acid crystallises in monoclinic prisms, it is readily soluble in water and alcohol but insoluble in ether. The solution in water is dextro-rotatory. When rapidly heated the acid melts at 167° to 170°. Heated with a little water to 175°, it gives a mixture containing much racemic and a little meso-tartaric acid ; at 165°, on the other hand, these proportions are reversed.

Inactivation of this kind is frequently met with among optically active compounds. The partial or complete conversion of optically active substances into inactive mixtures of the same constitution is known as *racemisation*, and may be effected with varying degrees of ease under the influence of heat, acids, alkalis or other reagents (see p. 35). In a few cases the change proceeds of itself in the apparently pure compound, the optical activity being completely lost in the course of time ; the phenomenon is then termed *auto-racemisation* [1] (see p. 35).

On being heated above its melting-point, *d*-tartaric acid parts with water and is transformed into anhydrides, which differ with the degree and duration of heating. At higher temperatures the mass becomes brown and develops a smell of caramel ; finally, charring sets in with the formation of a large number of decomposition products, including pyruvic and pyro-tartaric acids (pp. 260 and 275). When heated with hydriodic acid reduction takes place, first to malic acid and finally to succinic acid. The reduction to succinic acid may also be effected under the influence of certain bacteria.

Tartaric acid, cream of tartar and tartar emetic are used as mordants in dyeing and printing. The acid is also employed in the preparation of effervescing drinks, baking powder, and in the manufacture of artificial wine.

Salts of tartaric acid, tartrates.—The uses of *potassium hydrogen tartrate* (*cream of tartar*) have already been mentioned. On account of its comparative insolubility the formation of this compound serves as a laboratory test for potassium and tartaric acid. *Sodium potassium tartrate, Rochelle salt*, $KNaC_4H_4O_6+4H_2O$, is prepared from cream of tartar and sodium carbonate. It forms clear crystals, readily soluble in water. *Potassium antimonyl tartrate, tartar emetic,*

$$2[KOOC.CHOH.CHOH.COO(SbO)]+H_2O,$$

is obtained by boiling cream of tartar with antimony oxide. It is fairly easily soluble in water and acts as an emetic. It is used in conjunction with tannic acid as a mordant for basic dyestuffs. *Fehling's solution*, containing copper sulphate, Rochelle salt and

[1] See Walden, *Ber.*, 1898, **31**, 1416.

caustic soda,[1] is a useful reagent. When the deep blue solution is warmed with compounds possessing reducing properties a yellowish red precipitate of cuprous oxide is formed.

2. Laevo-tartaric acid, l-*tartaric acid*, is obtained by the resolution of racemic acid (see p. 39). In its chemical and nearly all its physical properties the *l*-acid is identical with the *d*-acid. It differs in rotating the plane of polarisation to the left to the same degree as *d*-tartaric acid rotates it to the right.[2] The salts of the two acids are very similar and generally isomorphous, but show opposed hemihedral facets. Salts with optically active bases, however, differ also in solubility.

3. Racemic acid, *para- or* dl-*tartaric acid*, sometimes occurs with the *d*-acid in grape juice and can be isolated from the argol mother-liquors. Its synthesis has already been mentioned, also its formation by oxidation of fumaric acid. It is composed of equimolecular proportions of *d*- and *l*-tartaric acids, and is formed by mixing solutions of these compounds.[3] The crystalline acid has the composition $2C_4H_6O_6+2H_2O$. Methods of resolving racemic acid into the active components have already been described on p. 38.

Racemic acid differs from the *d*- and *l*-acids in its optical inactivity and in forming rhombic prisms. It is less soluble than the active acids. On heating to 110°, water of crystallisation is expelled, and the anhydrous substance finally melts with effervescence at 205° to 206°. The salts, known as racemates, resemble those of tartaric acid but show no hemihedral facets. Potassium hydrogen racemate is more soluble than the corresponding active tartrate, but calcium racemate is less soluble than the calcium salts of the three other tartaric acids.

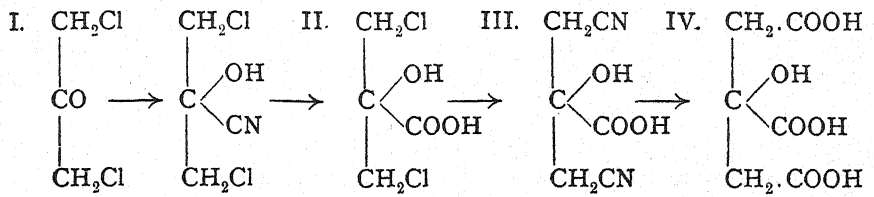
4. Meso-tartaric acid, $C_4H_6O_6+H_2O$, is formed by oxidation of maleic acid and by heating *d*-tartaric acid with water. It resembles racemic acid in being optically inactive, but unlike this compound cannot be resolved into active components. Meso-tartaric acid is therefore said to be *internally compensated* and racemic acid to be *externally compensated*. The anhydrous acid melts at 143°, considerably below the figure for racemic acid. Potassium hydrogen meso-tartrate is readily soluble in water.

Tribasic Hydroxy Acids

Citric acid, *hydroxy-tricarballylic acid*, $COOH.CH_2.C(OH)(COOH).CH_2.COOH+H_2O$, occurs in the free state in lemons, oranges, currants and other fruit. It is prepared on the large scale (*a*) from the juice of lemons, which contains about 6 to 7 per cent. of citric acid, by precipitation with milk of lime and decomposition of the calcium salt with sulphuric acid; (*b*) by fermenting sugars (*e.g.* cane sugar, glucose, maltose) with the aid of *Citromyces pfefferianus* and *Citromyces glaber*.

[1] The presence of tartaric acids prevents the precipitation of many metals by caustic soda. [2] Isomeric *d*- and *l*-modifications often differ in their physiological action. *l*-Tartaric acid, for example, is much more poisonous than the *d*-acid. [3] From cryoscopic measurements it appears that racemic acid in solution is decomposed into its components. The experiments of Cotton, however, indicate that some copper racemate exists as such in solution (see p. 32).

Synthetically, citric acid may be obtained from symmetrical dichloro-acetone (I), by treating it with hydrogen cyanide and hydrochloric acid to give dichloro-acetonic acid (II), and converting this by means of potassium cyanide into dicyano-acetonic acid (III), which on hydrolysis yields citric acid (IV).



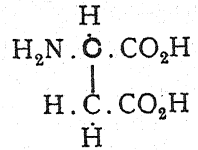
It crystallises in large rhombic prisms, dissolves readily in water and alcohol, but sparingly in ether. On heating it becomes anhydrous at 130° and melts at 153°. Above this temperature citric acid parts with water to form *aconitic acid* (see p. 280). If warmed carefully with concentrated sulphuric acid it decomposes into carbon monoxide, water and *acetone dicarboxylic acid*, $COOH.CH_2.CO.CH_2.COOH$.

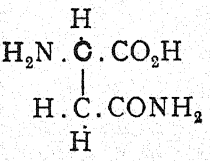
Citric acid is employed as a mordant in dyeing, and is used in the manufacture of lemonade.

Other polybasic hydroxy acids, such as *saccharic acids*, *manno-saccharic acids*, *mucic acid* and others, will be discussed under sugars.

Polybasic Amino-Acids

Certain representatives of this class are of interest owing to their occurrence among the hydrolytic products of proteins.

Aspartic acid, *amino-succinic acid*,  contains an asymmetric carbon atom and exists in three modifications, of which *l-aspartic* acid is the most important. It is found in beet molasses, and is formed as a hydrolysis product by the action of various reagents on animal and vegetable proteins. When treated with nitrous acid it is converted into *l*-malic acid, the amino group being replaced by a hydroxy group. By means of the Grignard reaction aspartic esters may be converted into amino-glycols.

Asparagine, the monoamide of amino-succinic acid,  occurs usually as the laevo variety in a number of plants, particularly in the embryo. It is found in asparagus, beetroot, and in large amount in the seeds of germinating lupins. The dextro-form is also present in the latter source. Optically active asparagines crystallise in clear rhombic

crystals, showing hemihedral facets; they differ in taste, *d*-asparagine being sweet, and the *l*-compound decidedly insipid.

On boiling with acids the amido group is hydrolysed and aspartic acid formed.

Glutamic acid, *α-amino-glutaric acid*, $CH_2<\begin{matrix}CH(NH_2).COOH\\CH_2.COOH\end{matrix}$, is formed together with aspartic acid by the hydrolysis of proteins with boiling dilute sulphuric acid; *e.g.* it constitutes about 30 per cent. of the crystalline products obtained from casein. The highest content (*ca.* 40 per cent.) of glutamic acid is given by certain plant proteins, the *prolamines*, occurring in grain. Glutamic acid is isolated by means of its very sparingly soluble hydrochloride. The acid and many of its salts are easily converted (*e.g.* even on heating to 185°) into pyrrolidone carboxylic acid, and are thus closely related to the cyclic amino-acid *proline* (p. 619).

Glutamine, the monoamide of glutamic acid, $C_3H_5(NH_2)(CONH_2)(COOH)$, is the nearest homologue of asparagine. In the inactive form it is found associated with the latter in beetroot, the embryo of the pumpkin, and other plants.

Hydroxy-glutamic acid, α-amino-β-hydroxy-glutaric acid, $COOH.CH(NH_2).CHOH.CH_2.COOH$, has been isolated from the hydrolysis products of proteins by Dakin,[1] by his method of extraction with butyl alcohol. It is crystalline, dissolves very readily in water, and on reduction with hydriodic acid yields glutamic acid. With phenols and concentrated sulphuric acid it gives various colour reactions.

Dibasic Aldehydic and Ketonic Acids

Mesoxalic acid, $CO(COOH)_2+H_2O$ or $C(OH)_2(COOH)_2$, is derived from malonic acid, and its constitution presents a problem similar to that of glyoxalic acid (p. 259). The compound cannot be obtained without the molecule of water quoted in the above formulæ, and it must therefore be assumed that this does not occur merely as water of crystallisation, but is united to the keto-group to form two hydroxyl groups. Nevertheless, the ketonic nature of the compound is clearly shown in its power of combining with alkali bisulphite, phenyl hydrazine and hydroxylamine, and also in its behaviour on reduction. Nascent hydrogen, for example, converts it into *tartronic acid*, $CHOH(COOH)_2$, containing a secondary alcoholic grouping. When boiled in aqueous solution, mesoxalic acid evolves carbon dioxide and yields glyoxalic acid, a reaction which is most readily explained by the hydroxy acid formula.

$$COOH.C(OH)_2.COOH = H.C(OH)_2.COOH+CO_2$$

The ethyl ester of mesoxalic acid is actually known to exist in the two forms, $C(OH)_2(COOEt)_2$ and $CO(COOEt)_2$.

Mesoxalic acid is most conveniently prepared by heating dibromomalonic acid with sodium hydroxide. It crystallises in deliquescent prisms, m.p. 121°.

[1] Dakin, *Biochem. J.*, 1918, **12**, 290.

Oxalo-acetic ester is produced by the condensation of oxalic and acetic esters: for the mechanism of this reaction, see p. 261 *et seq.*

$$\underset{\text{Oxalic ester}}{EtOOC.COOEt} + \underset{\text{Acetic ester}}{H_3C.COOEt} \longrightarrow \underset{\text{Oxalo-acetic ester.}}{EtOOC.CO.CH_2.COOEt}$$

The ester is a colourless oil which, like acetoacetic ester, may be regarded as a mixture of two tautomeric forms, viz.,

$$EtOOC.CO.CH_2.COOEt \text{ and } EtOOC.C(OH):CH.COOEt.$$

It undergoes hydrolysis in two ways. When boiled with alkalis, "acid hydrolysis" (I) takes place with the formation of oxalic acid, acetic acid and alcohol. On the other hand, boiling with dilute sulphuric acid brings about "ketonic hydrolysis" (II) into carbon dioxide and pyruvic acid. When heated alone, carbon monoxide is evolved and malonic ester formed (III).

I. $EtO_2C.CO.|CH_2.CO_2Et \longrightarrow HO_2C.CO_2H + CH_3.COOH + 2EtOH$

II. $EtO_2C.CO.CH_2.|CO_2Et \longrightarrow HO_2C.CO.CH_3 + CO_2 + 2EtOH$

III. $EtO_2C.|\overset{\cdots}{CO}|.CH_2.CO_2Et \longrightarrow EtO_2C.CH_2.CO_2Et + CO$

Acetone dicarboxylic acid, *β-keto-glutaric acid,* $HOOC.CH_2.CO.CH_2.COOH$, is obtained from citric acid by warming it with fuming sulphuric acid,

$$HO_2C.CH_2.C(OH)(CO_2H).CH_2.CO_2H = HO_2C.CH_2.CO.CH_2.CO_2H + CO + H_2O$$

or by oxidation with permanganate. It dissolves readily in water and in ether, and melts about 130° with decomposition into carbon dioxide and acetone. Four of the hydrogen atoms in acetone dicarboxylic acid can be replaced by sodium, since each methylene group lies between two carbonyl groups.

Oxalo-succinic ester, $CO(COOEt)—CH(COOEt)—CH_2(COOEt)$, is formed by condensing oxalic and succinic esters in the presence of sodium ethoxide. It exists in two liquid modifications, of which one (enolic) gives a deep red coloration with ferric chloride and the other (ketonic) gives none.[1]

Diaceto-succinic ester is prepared by the action of iodine on sodium acetoacetic ester (see p. 265). As has already been mentioned, it has proved of great service in the experimental investigation of tautomerism. The compound exists in desmotropic modifications which may be ketonic (I) or enolic (II) in structure, or a mixed form containing both arrangements.

I. $CH_3—CO—\underset{\displaystyle CH_3—CO—CH—COOC_2H_5}{\overset{|}{CH}}—COOC_2H_5$

II. $CH_3—C(OH)=\underset{\displaystyle CH_3—C(OH)=C—COOC_2H_5}{\overset{|}{C}}—COOC_2H_5$

XVII

Aldehydic and Ketonic Alcohols, Carbohydrates[2]

The carbohydrates are of the greatest importance from the theoretical as well as the practical standpoint. As foodstuffs they undoubtedly rank

[1] W. Wislicenus and Waldmüller, *Ber.*, 1911, 44, 1564. [2] *Cf.* E. Fischer, "Synthesen in der Zuckergruppe," *Ber.*, 1890, 23, 2114. E. F. Armstrong, *The Simple Carbohydrates and the Glycosides* (Longmans, Green). W. N. Haworth, *The Constitution of Sugars* (Arnold, 1929).

in the first place, and with the single exception of the proteins, no class of organic compounds is of such value in the study of the chemical processes which take place in plant and animal organisms. The term carbohydrate originally covered three groups of compounds, viz., those including glucose, $C_6H_{12}O_6$, cane sugar, $C_{12}H_{22}O_{11}$, and cellulose $(C_6H_{10}O_5)_n$ respectively. As may be seen from their formulæ, these substances are all composed of the three elements carbon, hydrogen and oxygen, united in characteristic manner. The number of carbon atoms is six or a multiple of six, and there are twice as many hydrogen atoms as oxygen atoms in the molecule. The last two elements are therefore present in the proportions required to form water, a peculiarity which gave rise to the term *carbohydrate*. Later, however, as the classical researches of Emil Fischer threw more light on the constitution of these compounds, and the great number of examples already known became increased by the addition of numerous synthetic products, the conception of the term carbohydrate had to be expanded and a new nomenclature introduced. Before going into the question in detail, it may be remarked that the carbohydrates of the glucose group, $C_6H_{12}O_6$, contain two hydrogen atoms less than the hexahydric alcohols, $C_6H_{14}O_6$ (see p. 252), and from their chemical character are divided into *aldehydic alcohols* and *ketonic alcohols*. A simpler example of an aldehydic alcohol is glycollic aldehyde, $CH_2OH.CHO$, and of a ketonic alcohol, dihydroxy-acetone, $CH_2OH.CO.CH_2OH$.

The first division of the carbohydrates is into three main classes according to their complexity, viz. :

A. *Monosaccharides*, *e.g.* arabinose, $C_5H_{10}O_5$, glucose, $C_6H_{12}O_6$.
B. *Di-* and *tri-saccharides*, *e.g.* cane sugar, $C_{12}H_{22}O_{11}$, raffinose $C_{18}H_{32}O_{16}$.
C. *Higher polysaccharides*, *e.g.* starch, cellulose, $(C_6H_{10}O_5)_n$.

Owing to their sweet taste and crystalline character the mono-, di- and tri-saccharides are generally grouped together under the name of *sugars*. The character of a monosaccharide, originally associated with the presence of six carbon atoms in the molecule, is nowadays determined mainly by its constitution as an aldehydic alcohol containing the group $-CHOH.CH:O$, or as a ketonic alcohol with the group $-CO.CH_2OH$. In this class are included not only those compounds with six carbon atoms, but many with a smaller or greater number than this. A further distinction is drawn between aldehydic and ketonic sugars by use of the terms *aldoses* and *ketoses*. The number of oxygenated carbon atoms present in the molecule is indicated by adding the necessary prefix to the termination *-ose*. In this way monosaccharides are subdivided into the smaller classes of *bioses*, *trioses*, *tetroses*, *pentoses*, *hexoses*, *heptoses*, *octoses* and *nonoses*. Since, however, the members of these groups may be either aldehydes or ketones, this is expressed by use of the prefix *aldo-* or *keto-* respectively. For example, glyceric aldehyde, $CH_2OH.CHOH.CHO$, is an *aldotriose*, and dihydroxy-acetone, $CH_2OH.CO.CH_2OH$, a *ketotriose*.

The polysaccharides appear to be anhydrides or ether derivatives of the monosaccharides. If they are formed from 2 mols. of the monosaccharide by loss of 1 mol. water they are termed *disaccharides*, *e.g.* cane sugar, $C_{12}H_{22}O_{11}$. Raffinose, $C_{18}H_{32}O_{16}$, is a *trisaccharide* formed from three monosaccharide molecules by elimination of 2 mols. water. Generalising these formulæ, we obtain $nC_6H_{12}O_6-(n-1)H_2O$. If n is very large, the factor $n-1$ approximates to n, and we have

$$nC_6H_{12}O_6-nH_2O = n(C_6H_{12}O_6-H_2O) = n(C_6H_{10}O_5)$$

The latter is the formula for the higher polysaccharides, including starch and cellulose. All polysaccharides undergo hydrolysis, taking up water to form monosaccharides.

I.—MONOSACCHARIDES [1]

The number of monosaccharides known is in the neighbourhood of fifty, of which ten occur in nature and the remainder are synthetic. The existence of such a large number of compounds is due to the presence of asymmetric carbon atoms within the molecules. Aldohexoses, for example, which include glucose, a sugar of great historical and practical interest, contain no less than four asymmetric atoms, each of which may be present in either the *d*- or *l*- configuration. It has already been shown on p. 33 how rapidly the number of stereoisomerides increases with each additional asymmetric atom.

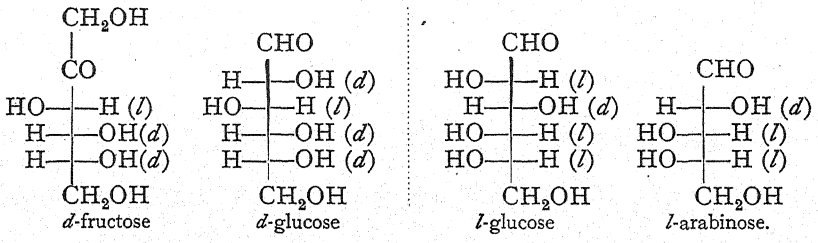
A list of the best known monosaccharides is given below.

Biose	$CH_2OH.CHO$, glycollic aldehyde.
Trioses	1. $CH_2OH.CHOH.CHO$, glyceric aldehyde.
	2. $CH_2OH.CO.CH_2OH$, dihydroxy-acetone.
Tetroses	$CH_2OH.(CHOH)_2.CHO$, erythrose.
Pentoses	$CH_2OH.(CHOH)_3.CHO$, arabinose, xylose, ribose.
Methyl-pentose	$CH_3.(CHOH)_4.CHO$, rhamnose.
Hexoses	1. $CH_2OH.(CHOH)_4.CHO$, glucose, gulose, mannose, galactose, talose.
	2. $CH_2OH.(CHOH)_3.CO.CH_2OH$, fructose, sorbose.
Heptoses	$CH_2OH.(CHOH)_5.CHO$, mannoheptose, glucoheptose, galaheptose.
Octoses	$C_8H_{16}O_8$.
Nonoses	$C_9H_{18}O_9$.

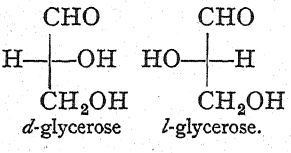
An explanation is required as to the way in which the optical isomerides are named. In accordance with a suggestion of Fischer, the structure of the sugars is, wherever possible, referred back to that of the active glucoses. Any other monosaccharide standing in close structural relationship to one or other of the glucoses is generally labelled with the corresponding letter *d*- or *l*-, irrespective of the actual sign of its rotation. Ordinary fructose, for example, which is lævorotatory, is commonly termed *d*-fructose, owing to its spatial relationship to *d*-glucose; and naturally occurring arabinose, which is dextrorotatory, is termed

[1] For the connection between the constitution of aliphatic compounds and their sweetness of taste see E. Oertly and R. G. Myers, *J. A. C. S.*, 1919, 41, 855.

l-arabinose to indicate its relationship to *l*-glucose. This is illustrated in the following formulæ, in which the terminal aldehydic or ketonic group is written uppermost and the links binding the H and OH addenda are assumed to be inclined from the chain of central carbon atoms towards the observer. According to the usual convention a CHOH group having the hydroxyl on the right of the formula is then regarded as being of the *d*-configuration and *vice versa*. In the following pages the asymmetric carbon atoms are omitted and simplified projection formulæ employed.



In some cases the actual sign of the rotation given by a compound is indicated in the following pages by the use of the signs + and —, *e.g.* *d*(—)-fructose for ordinary fructose. In addition, the prefix *dl*- indicates a racemic and *i*- a meso form.



Wohl's work on glycerose now enables the family relationships to be carried back to the *d*- and *l*-glyceroses, from which all other sugars can be derived by extending the molecule on the side of the aldehyde group by reaction with HCN (see p. 293). The nomenclature fortunately remains unchanged, as *d*-glycerose is *d*-rotatory and is *genetically related* to *d*-glucose. Hence it will be seen that the family of a sugar is determined in each case by the spatial arrangement of the CHOH group adjacent to the terminal CH_2OH, no matter what the disposition of the rest of the molecule may be (*cf.* table on p. 303). If this group has a dextro configuration, as indicated by writing it with the OH to the right, the sugar is classified as belonging to the *d*-family.

The same system is applied to other derivatives of the monosaccharides.

General Properties and Methods of Formation

The monosaccharides are sweet-tasting compounds, the chemical behaviour of which may be deduced from their structure as aldehydic or ketonic alcohols.

As alcohols they unite readily with acids to form **esters,** *e.g.* acetic anhydride converts them into acetyl derivatives, and with nitric acid at 0° they form nitrates. The *phosphoric esters of pentoses and hexoses* are of great physiological importance, the former as disruption products of many nucleic acids (p. 803) and the latter as being essential for the

biological degradation of carbohydrates, *e.g.* in alcoholic fermentation and during muscular effort [1] (see pp. 318 and 319). With inorganic bases such as sodium hydroxide or strontium hydroxide the monosaccharides yield *derivatives*,[2] those from glucose, for example, being known as glucosates.

As aldehydes or ketones they are characterised by numerous reactions, only the more important of which need be quoted. On **reduction** they take up two atoms of hydrogen and pass into the corresponding alcohols ; from a pentose is obtained a pentitol or pentahydric alcohol, and from a hexose a hexitol or hexahydric alcohol. On **oxidation** they yield carboxylic acids. Cautious oxidation converts aldoses first into the corresponding monocarboxylic acids containing the same number of carbon atoms, aldopentoses being transformed into pentonic acids, $CH_2OH.(CHOH)_3.COOH$, and aldohexoses into hexonic acids, $CH_2OH.(CHOH)_4.COOH$. With stronger oxidising agents the process may go further and hexoses, for example, may be oxidised to the corresponding stereoisomeric saccharic or tetra-hydroxy-adipic acids, $COOH.(CHOH)_4.COOH$. As would be expected, the ketoses on oxidation yield acids containing a smaller number of carbon atoms. The **reducing properties** of the monosaccharides are shown in their behaviour with ammoniacal silver nitrate solution, from which silver is precipitated, and particularly with Fehling's solution, from which on warming a reddish precipitate of cuprous oxide is thrown down. This behaviour is characteristic of ketoses as well as aldoses. In the absence of other reducing agents the last reaction may be employed not only for the qualitative detection of the monosaccharides, but also for their quantitative estimation. Aldoses may also be distinguished from ketoses by giving a pink colour with sensitised Schiff's reagent (Tokie, *Ind. Eng. Chem.* [Anal.], 1942, **14**, 405).

On warming with alkalis the monosaccharides give yellowish-brown solutions and finally resinify.

The presence of a sugar can often be determined qualitatively by certain colour reactions. Among these may be mentioned the *formation of furfural* (see index) by the action of aqueous hydrochloric acid upon pentoses. If a paper previously treated with aniline acetate is held in the escaping vapours, it develops a red coloration.

Molisch's test is also a general one. This consists in adding to the sugar solution one or two drops of a solution of α-naphthol, and pouring down the side of the vessel a little concentrated sulphuric acid (free from nitric acid). The furfural derivatives formed by the action of sulphuric acid produce a violet coloration at the junction of the two liquids, either in the cold or on gentle warming.

Some of the more important processes which have been devised for studying the relationships among the simpler carbohydrates are described in the following pages.

[1] Compare A. Harden and W. J. Young, *Proc. Chem. Soc.*, 1905, **21**, 189. G. Embden and M. Zimmermann, *Zeit. physiol. Chem.*, 1927, **167**, 114. [2] E. G. V. Percival, *J. C. S.*, 1934, 1160.

Osazones and the Conversion of Aldoses into Ketoses

As aldehydes or ketones the monosaccharides also react with hydrazines and hydroxylamine. *Phenyl-hydrazine*, $C_6H_5NHNH_2$, has proved of the greatest value in the separation, identification and interconversion of the various monosaccharides. Without the aid of this reagent the brilliant researches of Fischer in the sugar group would hardly have been possible.

When 1 mol. of phenyl-hydrazine reacts with 1 mol. of an aldose or ketose, the first product is a normal hydrazone (see p. 181).

$$\underset{\text{Glucose}}{CH_2.OH[CH.OH]_4.CH:O} + H_2N.NHC_6H_5 = \underset{\text{Glucose phenyl-hydrazone.}}{CH_2.OH[CH.OH]_4.CH:N.NHC_6H_5} + H_2O$$

On warming with excess of phenyl-hydrazine, however, the hydrazone first formed is oxidised in such a way that the CH.OH group adjacent to the original aldehydic or ketonic group is converted into a CO group.[1] The latter then combines with more phenyl-hydrazine to give a di-hydrazone [2] containing the group I. These compounds are termed **osazones.**

I. $CH:N.NH.C_6H_5$ / $C:N.NH.C_6H_5$

$CH:N.NH.C_6H_5$ / $C:N.NH.C_6H_5$ / $(CHOH)_3$ / CH_2OH Glucosazone.

Prior to Fischer's researches one of the greatest barriers to a wider knowledge of the monosaccharides lay in the difficulty of separating mixtures of these sugars by crystallisation, owing to their high solubility in water and tendency to form syrups. The value of the osazones depends on the fact that they are sparingly soluble, and easily separable by crystallisation; and, in addition, from their characteristic melting-points and crystalline forms as seen under a microscope it is possible to identify the parent sugar with ease and certainty.

The *recognition and isolation of ketoses* is a matter of some difficulty owing to their lack of characteristic reactions. With secondary hydrazines of the type of phenyl-methyl hydrazine, however, the ketoses give phenyl-methyl osazones by which they may be identified (Neuberg, *Ber.*, 1902, **35**, 959, 2626). Aldoses usually react with this base to form colourless hydrazones, which in all cases are easily distinguished or separated from the highly coloured osazones.

Osazones, like all hydrazones, are hydrolysed on being heated with hydrochloric acid, when phenyl-hydrazine is regenerated. The sugar originally employed, however, is not regained, as the group

$$—C(:N.NH.C_6H_5)—CH(:N.NH.C_6H_5)$$

[1] In this reaction phenyl-hydrazine removes two atoms of hydrogen from the sugar and is converted into aniline and ammonia: $C_6H_5.NH.NH_2 + 2H = C_6H_5.NH_2 + NH_3$. [2] These compounds are probably cyclic in structure, *cf.* p. 305.

is converted into the group —CO.CHO. The compound so formed is thus an oxidation product of the original sugar, and is termed an **osone.** In the example quoted above glucose yields

$$CH_2OH.(CHOH)_3.CO.CHO$$
Glucosone.

On mild reduction of this compound with zinc dust and dilute acetic acid the aldehydic group alone is attacked and converted into an alcoholic group, the keto group remaining unchanged. In this case, therefore, the sugar finally obtained is fructose, in place of the glucose used as starting material.

$$CH_2OH.(CHOH)_3.CO.CH_2OH$$
Fructose.

In these reactions we have a *general method of transforming an aldose into a ketose*, according to the scheme

$$\text{Aldose} \xrightarrow[\text{Hydrazine}]{\text{Phenyl}} \text{Osazone} \xrightarrow{\text{Hydrolysis}} \text{Osone} \xrightarrow{\text{Reduction}} \text{Ketose}$$

Degradation and Synthesis of Aldoses

Monosaccharides react with hydroxylamine to yield oximes, the aldehydic or ketonic oxygen being replaced by the group : N.OH. By use of these compounds Wohl devised a method of effecting the *degradation of a higher aldose to one of lower carbon content.* For example, glucose forms the oxime $CH_2OH.(CHOH)_4.CH : NOH$, which on being heated with acetic anhydride parts with water and is converted into the acetyl derivative of the nitrile $CH_2OH(CHOH)_4CN$. The latter on treatment with ammoniacal silver nitrate is decomposed, yielding hydrogen cyanide and the corresponding aldopentose, *d*-arabinose. The acetyl groups are hydrolysed at the same time.

$$CH_2OH.(CHOH)_3.CHOH.CN \longrightarrow HCN+CH_2OH.(CHOH)_3.CH:O$$

Aldoses may also be degraded by Ruff's method by converting them into the corresponding monobasic acids, *e.g.* $CH_2OH.(CHOH)_4.COOH$, and oxidising the latter in the form of their calcium salts with hydrogen peroxide and a trace of a ferric salt (*Fenton's reagent*). In this reaction the carboxyl group is eliminated as carbon dioxide, and at the same time the adjacent alcoholic group is oxidised to aldehyde.

$$CH_2OH.(CHOH)_3.CHOH.COOH+O \longrightarrow CH_2OH.(CHOH)_3.CHO+CO_2+H_2O$$

Monosaccharides, as aldehydes and ketones, also unite with hydrogen cyanide to form cyanhydrins. By use of this reaction, which is due to Kiliani, we may effect the *synthesis of a higher from a lower aldose.* The cyanhydrins are first hydrolysed to hydroxy-acids, which are readily converted into lactones. The latter are then reduced to aldoses by means

of sodium amalgam and dilute sulphuric acid. Glucose, $C_6H_{12}O_6$, under these conditions yields a new sugar, gluco-heptose, $C_7H_{14}O_7$.

$$\underset{\text{Glucose}}{CH_2OH.[CHOH]_4.CH{:}O} + HCN \longrightarrow \underset{\text{Glucose cyanhydrin}}{CH_2OH.[CHOH]_4.CHOH.CN}$$

$$\xrightarrow{\text{Hydrolysis}} \underset{\text{Glucose carboxylic acid}}{CH_2OH.CHOH.CHOH.CHOH.CHOH.CHOH.COOH} \xrightarrow{-H_2O}$$

$$CH_2OH.CHOH.CHOH.CH.CHOH.CHOH.CO \quad (\text{lactone ring: O})$$

Lactone of glucose carboxylic acid

$$\xrightarrow{2H} \underset{\text{Gluco-heptose.}}{CH_2OH.CHOH.CHOH.CHOH.CHOH.CHOH.CH{:}O}$$

In a similar manner gluco-heptose may be used to build up an octose. The synthesis has been carried as far as the nonoses.

Conversion of Ketoses into Aldoses

In this connection a series of reactions may be mentioned by means of which it is possible to pass from *ketoses into aldoses*. The ketose is reduced to the corresponding alcohol, which on oxidation yields a monobasic acid. This in turn readily passes into the lactone, from which an aldose is obtained by reduction with sodium amalgam in weakly acid solution, *e.g.*

$$\underset{\text{Ketohexose}}{CH_2OH(CHOH)_3.CO.CH_2OH} \xrightarrow{\text{Reduction}} \underset{\text{Hexitol}}{CH_2OH(CHOH)_3.CHOH.CH_2OH}$$

$$\xrightarrow{\text{Oxidation}} \underset{\text{Hexonic acid}}{CH_2OH(CHOH)_3.CHOH.COOH}$$

$$\xrightarrow{H_2O \text{ eliminated}} CH_2OH.CHOH.CH.CHOH.CHOH.CO \quad (\text{lactone ring: O})$$

Lactone of the hexonic acid

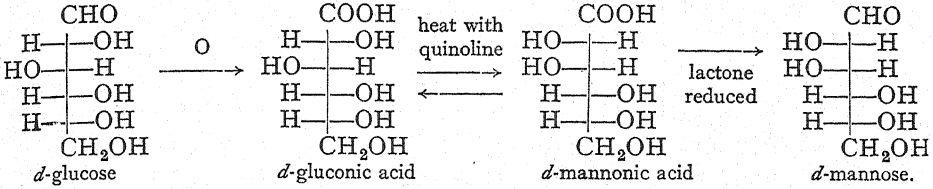
$$\xrightarrow{\text{Reduction}} \underset{\text{Aldohexose.}}{CH_2OH.(CHOH)_3.CHOH.CH{:}O}$$

Epimerisation

In synthetic work with the aldoses considerable use has been made of a process termed *epimerisation*,[1] which partially or completely reverses the configuration of the CHOH group in the α-position to the terminal aldehyde grouping (*cf.* p. 37). The aldose is first oxidised to the corresponding monocarboxylic acid, which is then heated with aqueous quinoline or pyridine, when the inversion of the α-group is more or less completely effected. On converting the new acid into the corresponding

[1] *Epimers* (epimerides) are substances containing several asymmetric centres and differing only in the configuration of *one* of these.

lactone, followed by reduction, a new aldose is obtained. This process may be illustrated by the transformation of glucose into mannose.

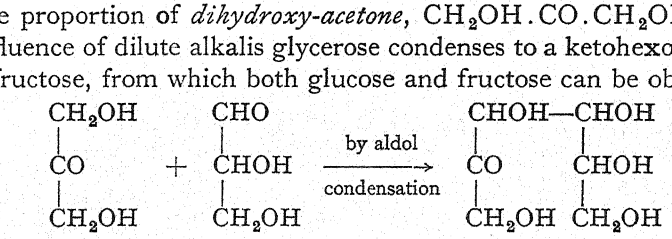


In this manner a number of new aldoses have been prepared.

Synthesis of Monosaccharides

Monosaccharides have been prepared artificially by the following methods :

1. A valuable starting-point for the synthesis of natural sugars was discovered by E. Fischer in glycerol. On careful oxidation with nitric acid, or with bromine water and sodium carbonate, glycerol yields a product which gives the reactions of the monosaccharides and is therefore known as *glycerose*. Among other constituents this substance contains a large proportion of *dihydroxy-acetone*, $CH_2OH.CO.CH_2OH$. Under the influence of dilute alkalis glycerose condenses to a ketohexose, *α-acrose* or *dl*-fructose, from which both glucose and fructose can be obtained.



Aldoses and ketoses may also be formed quite generally by oxidation of the corresponding alcohols (for example, with nitric acid, sodium hypobromite, hydrogen peroxide and ferrous sulphate, or lead peroxide and hydrochloric acid). In this way arabinose, $C_5H_{10}O_5$, may be obtained from arabitol, $C_5H_{12}O_5$, and mannose from mannitol.

2. The same α-acrose that is formed from glycerose can also be prepared from formaldehyde. On allowing the latter to remain in contact with lime-water it undergoes the aldol condensation (see p. 180), and amongst other compounds a mixture of sugars of the formula $C_6H_{12}O_6$ is produced, known as *formose*, from which α-acrose may be isolated.

$$H_2C:O+HCH:O+HCH:O+HCH:O+HCH:O+HCH:O$$
$$= H_2C.OH—CH.OH—CH.OH—CH.OH—CH.OH—CH:O$$

3. The formation of monosaccharides by the hydrolysis of polysaccharides with dilute acids has been mentioned on p. 289, *e.g.*,

$$C_{12}H_{22}O_{11}+H_2O = 2C_6H_{12}O_6$$

4. Higher aldoses may be built up from lower members by the cyanhydrin method (see p. 293).

Sugars prepared by complete synthesis in the laboratory are always first obtained in an optically inactive form, whereas those produced in plants by the assimilation of carbon dioxide are active. Laboratory methods, however, also yield active products if optically active materials take part in the reaction (see asymmetric synthesis, p. 45). This is what occurs in the natural process, since the conversion of carbonic acid into sugar is undoubtedly brought about in collaboration with the optically active substances of the chlorophyll nucleus. There is therefore no fundamental difference between the artificial and natural synthesis of optically active compounds.

1. Bioses, Trioses and Tetroses

The simplest example of this group is **glycollic aldehyde,** $CH_2OH.CHO$, which can be obtained from glycol by oxidation with hydrogen peroxide, or from bromoacetaldehyde, $CH_2Br.CHO$, by treatment with baryta. It is a syrup of somewhat sweet taste. The two trioses, **glyceric aldehyde** and **dihydroxy acetone,** have already been mentioned (pp. 250, 295). The former is prepared by oxidation of acrolein acetal and hydrolysis of the resulting acetal of glyceric aldehyde. It occurs in a stable dimolecular form, m.p. 138°, which in aqueous solution is slowly transformed into an enolic syrupy monomolecular form.[1] *Dihydroxy acetone* is a crystalline compound, m.p. 68-75°, which is soluble in water and has a sweet taste. With sodium amalgam it is readily reduced to glycerol.

Glycollic aldehyde and glyceric aldehyde differ from higher aldoses in the ease with which they polymerise to compounds of twice their molecular weight. In other ways also the aldehydic character is more pronounced than with the higher sugars. Among the tetroses, *dl*-**erythrose** is obtained by oxidation of the corresponding alcohol *i*-erythritol, and by the condensation of glycollic aldehyde. In the former case the product consists mainly of a mixture of aldotetrose and ketotetrose ; in the latter case the aldotetrose is probably formed.

Additional methods of preparing tetroses include the *degradation of pentoses* by way of the oximes (see p. 293), and the *oxidation of pentonic acids* (in the form of their calcium salts) with hydrogen peroxide in the presence of a trace of ferric salt (p. 293).

2. Pentoses

Aldopentoses of the formula

$$CH_2OH.CHOH.CHOH.CHOH.CH:O$$

contain three asymmetric carbon atoms, and according to theory should therefore exist in eight optically active and four racemic forms. Two of these, l-*arabinose* and d-*xylose*, occur in the combined state in the vegetable kingdom in the complex polysaccharides *pentosans*, and in the form of glycosides : d-*ribose* is found as a constituent of the nucleoproteins (p. 804). These naturally occurring sugars are described below. Other pentoses have been prepared synthetically.

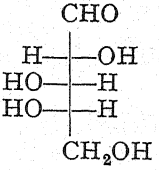
In their chemical behaviour pentoses possess the general properties of the monosaccharides, but in addition give characteristic reactions by

[1] Wohl, *Ber.*, 1898, **31**, 1796, 2394. See also H. G. Reeves, *J. C. S.*, 1927, 2477.

which they are easily recognised and distinguished from hexoses. For example, when heated with diluted hydrochloric or sulphuric acid they yield *furfural*, $C_5H_4O_2$ (methyl pentoses give methyl furfural), which forms sparingly soluble derivatives with phenyl-hydrazine, pyrogallol and barbituric acid. This reaction is used in the quantitative estimation of pentoses.[1] A qualitative test for pentoses consists in heating them with *hydrochloric acid and phloroglucinol*, when a cherry-red coloration is produced.

The pentoses do not undergo fermentation.

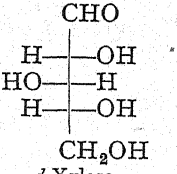
l(+)**Arabinose,**[2] is obtained together with xylose by boiling gum arabic, cherry gum, or the pith of maize and elder with dilute sulphuric acid (hydrolysis of pentosans). It forms prisms, m.p. 160°, and is dextrorotatory. On reduction it yields l-*arabitol*, and on oxidation passes first into l-*arabonic acid*, $CH_2OH.(CHOH)_3.COOH$, and finally into l-*trihydroxy-glutaric acid*, $COOH.(CHOH)_3.COOH$.



l-Arabinose.

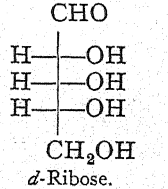
d(−)**Arabinose,** the optical antipode of the above compound, is produced by the degradation of *d*-glucose-oxime or of *d*-gluconic acid. *dl*-**Arabinose,** m.p. 164°, is formed by combination of the two optically active components and is possibly the pentose which is present in human urine in cases of pentosuria.

d-**Xylose,** or wood sugar, can be obtained from a variety of vegetable products, *e.g.* by boiling bran, wood or straw with dilute acids. It is best prepared from maize cobs.[3] It is dextrorotatory, and on reduction yields *i*-xylitol. When oxidised it gives first *d*-xylonic acid and finally *i*-trihydroxy-glutaric acid. *d*-Xylose is also formed by the degradation of *d*-gulonic acid, and by synthetic methods may be converted into *d*-gulose. When degraded through the oxime it yields *d*-threose, which is oxidisable to *l*-tartaric acid. These reactions lead to the above configuration for *d*-xylose.



d-Xylose.

d-**Ribose** is present in certain nucleic acids[4] (p. 804). It forms the same osazone as *d*-arabinose, and therefore has the configuration given.



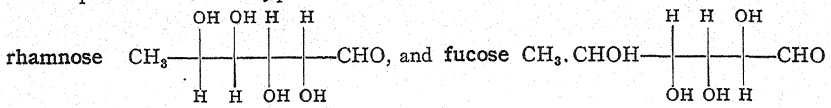
d-Ribose.

Arabinose and xylose exhibit mutarotation (see p. 94), *i.e.*, the rotation of a freshly prepared solution changes with time until a constant value is attained. In both these cases the rotation diminishes. An explanation of this peculiarity is given on p. 300.

Other widely distributed members of this group are the *methyl-pentoses*, which are found in polysaccharides and glycosides of vegetable origin.

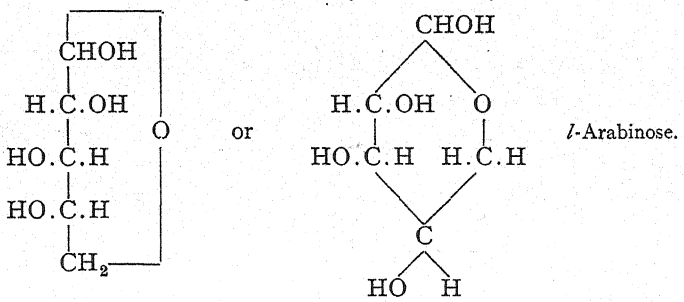
[1] *Ber.*, 1902, **35**, 4440. Jolles, *Ann.*, 1907, **351**, 38. For furfural see index. [2] For further information concerning the methods by which the configurations of the pentoses and hexoses have been derived see Armstrong, *The Simple Carbohydrates and the Glycosides* (Longmans); Haworth, *The Constitution of Sugars* (Arnold, 1929). [3] K. P. Monroe, *J. A. C. S.*, 1919, **41**, 1002. [4] Levene and Jacobs, *Ber.*, 1909, **42**, 1476.

Compounds of this type are



Rhamnose occurs in many glycosides and has played an important part in connection with the stereochemistry of sugars. The question of its configuration was settled by Fischer and Zach's synthesis of *iso*-rhamnose,[1] the first synthesis of a methyl-pentose to be effected. Fucose is a constituent of many vegetable polysaccharides.

For simplicity of presentation the pentoses have been represented in the foregoing pages as open-chain sugars. The work of Haworth, however, leaves no doubt that they actually exist in cyclic structures of



l-Arabinose.

the ether type containing a 6-membered ring (see p. 301). *l*-Arabinose is therefore more correctly formulated by either of the above structures, in which, as before, a CHOH group of the dextro configuration is written with the OH to the right.

3. The Hexoses and Glycosides

Cyclic Structure of Monosaccharides

Hexoses are compounds of sweet taste, which are generally difficult to obtain in the crystalline state. They are very soluble in water, sparingly soluble in absolute alcohol, and insoluble in ether. The study of this group provided an admirable opportunity of putting stereochemical theory to an exacting test, from which it has emerged unscathed.

The **aldohexoses**, $CH_2OH.CHOH.CHOH.CHOH.CHOH.CH:O$, contain four asymmetric atoms, and according to theory should exist in sixteen optically active isomerides, consisting of eight pairs of enantiomorphs. All of these compounds are known,[2] and their configurational formulæ are given on p. 303. It is now generally accepted that each of these stereoisomerides normally exists in a cyclic form having an oxidic or inner ether structure. Information on this point has been gathered chiefly from two sources, namely the study of glycosides and

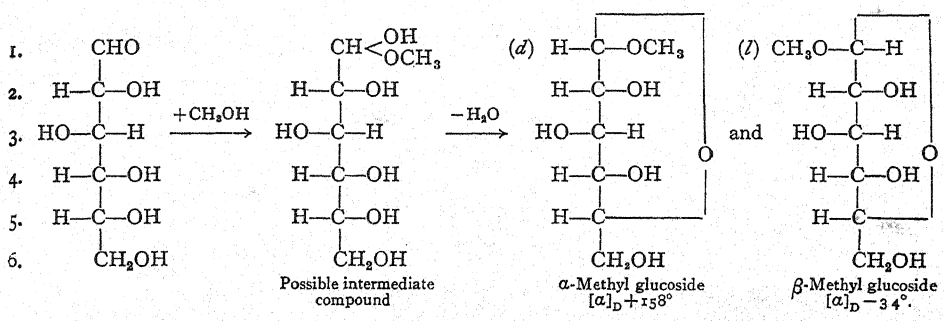
[1] *Ber.*, 1912, 45, 3761. [2] The two aldohexoses, *l*-altrose and *l*-allose, have only recently been isolated, see W. C. Austin and F. L. Humoller, *J. A. C. S.*, 1934, **56**, 1153.

the researches on methylated sugars initiated many years ago by Purdie and developed with conspicuous success by Irvine and Haworth.

A hexose such as glucose combines with methyl alcohol in the presence of hydrogen chloride to form a mixture of two stereoisomeric methyl-glycosides.[1] These compounds do not react with phenyl-hydrazine and hence contain no free aldehyde group. Although comparatively stable

$$C_6H_{12}O_6+CH_3OH = C_6H_{11}O_5.OCH_3+H_2O$$

towards alkalis, they are readily hydrolysed by hot dilute acids. It is evident therefore that the aldehyde group is now united to alcohol in the same manner as in the acetals (see p. 178). But since only one molecule of alcohol enters into combination with a molecule of glucose, with loss of one molecule of water, it must be assumed that an alcoholic group of the sugar also takes part in the process, to form a cyclic anhydride.



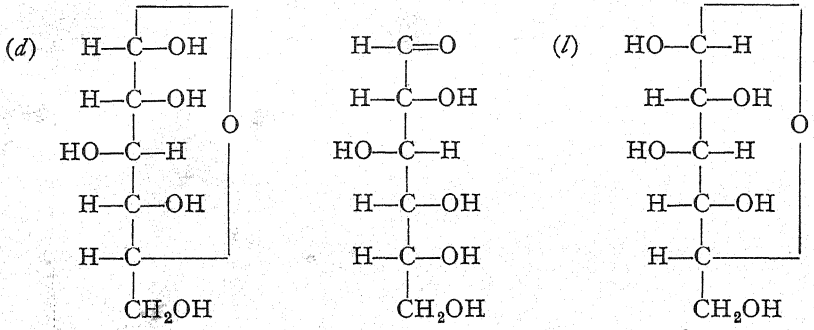
It will be seen that the end carbon atom (1) has now become asymmetric and can thus exist in either the *d*- or *l*-configuration. There will therefore be two stereoisomeric glucosides, which are distinguished as the α- and β-forms. The actual hydroxyl group engaged in ring-formation was extremely difficult to identify with certainty, and at first it was assumed, by analogy with the lactones of γ-hydroxy acids, that the union was to the C-atom in position 4. A cyclic structure of this kind is described as containing a butylene oxide or 1 : 4-oxidic ring.[2] Later research has shown that these compounds actually contain a 1 : 5- or amylene oxide link as illustrated in the above formulæ.

The behaviour of glucose in undergoing mutarotation led to the suggestion that the free sugar also occurred in cyclic forms corresponding to the α- and β-glucosides, and that mutarotation was due to the partial conversion of one form into the other through an intermediate open-chain glucose.

Definite proof of the existence of α- and β-glucoses was first obtained by E. F. Armstrong.[3] In common with other α- and β-glucosides the methyl glucosides show characteristic differences in their behaviour

[1] E. Fischer, *Ber.*, 1893, **26**, 2400. Compounds of this type are now described under the general heading of **glycosides.** Each individual product is named after the particular sugar present, *e.g.* glucosides from glucose, fructosides from fructose and maltosides from maltose (see p. 308). [2] This inner ether or lactone structure was first suggested by Tollens. [3] E. F. Armstrong, *J. C. S.*, 1903, **85**, 1306. Lowry, *J. C. S.*, 1904, **87**, 1551.

towards certain hydrolytic enzymes. *Maltase*, an enzyme which is present in yeast and various other sources, rapidly hydrolyses α-methyl glucoside in aqueous solution to methyl alcohol and glucose, but has no influence on the β-glucoside. On the other hand, the latter is readily hydrolysed by the enzyme *emulsin*, which is present in bitter almonds. Emulsin, however, does not attack the α-compound. By this means glucosides



α-*d*-Glucose
$[\alpha]_D$ +110°

Possible intermediate form

β-*d*-Glucose
$[\alpha]_D$ +17·5°.

have been classified as α- and β-glucosides, according to their behaviour towards these enzymes. Armstrong demonstrated the existence of a similar isomerism in the free sugar by showing that two glucoses of different rotatory powers were formed when α- and β-methyl glucosides respectively were hydrolysed by enzymes. The α-glucose liberated from the α-glucoside has a high rotation, whereas β-glucose from the β-glucoside has a very low value. In a short time, or more rapidly on addition of ammonia, each of the newly liberated forms changes into the same equilibrium mixture of α- and β-glucoses having a rotation of intermediate value. Hence the mutarotation of glucose is due to intramolecular change. Subsequently it was found that by recrystallising ordinary glucose under suitable conditions (p. 305) it is possible to convert it into the pure α- or β-glucose, the rotations of which (prior to mutarotation) are appended to the above formulæ.

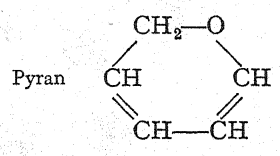
In 1914 Emil Fischer [1] discovered a third form of methyl glucoside, which he described as a γ-form in order to distinguish it from the previously known α- and β- varieties. A year later Irvine isolated a tetramethyl γ-glucose [2] (*i.e.* a γ-glucose having four OH groups replaced by OCH_3) which was extremely reactive; it combined very readily with alcohol and resembled the γ-glucoside in instantly decolorising alkaline permanganate solution. Irvine also showed that Fischer's γ-glucoside was a mixture of two stereoisomeric forms (*cf.* α- and β-methyl glucosides) but found that the corresponding γ-glucose was too labile to be isolated. Owing to its unstable nature the γ-glucose grouping in these compounds was formulated as possessing a different type of ring structure to that present in the α- and β-glucoses and glucosides.

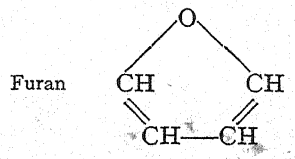
[1] *Ber.*, 1914, **47**, 1980. [2] Irvine, Fyfe and Hogg, *J. C. S.*, 1915, **107**, 524.

Later research by Haworth and his co-workers on methylated monosaccharides and lactones of hydroxy acids (see below) has shown that the ordinary *pentoses and hexoses normally exist in the* 1:5- *or amylene oxide form* and that the *labile γ-sugars possess a* 1:4- *or butylene oxide ring*. These conclusions are based upon the following lines of argument: (1) a study of the relationships existing between the rotatory powers of the various methylated and unmethylated sugars, (2) the conversion of the monosaccharides into their completely methylated forms, followed by an investigation of the products given by the latter on oxidation, and (3) a study of the rates with which the lactones of the series are hydrolysed to form the open-chain acids. Haworth has shown that among the lactones of the carboxylic acids, the δ-lactones as a class are much more rapidly hydrolysed in water than the γ-lactones.

As an example of Haworth's methods we may quote the case of glucose.[1] The α- and β-methylglucosides I (prepared from glucose) were methylated to give the normal crystalline tetramethyl glucose II and this on mild oxidation was converted into the corresponding lactone IV, which from its rate of hydrolysis was characterised as a δ-lactone having the oxygen bridge in the 1:5- position. A similar amylene oxide structure may be assumed for the original sugar. Further confirmation of the correctness of these deductions is obtained by the oxidation of the lactone IV to xylotrimethoxyglutaric acid V by means of concentrated nitric acid. (For formulæ I-V, see next page.) Similar methods have been applied to other aldoses and ketoses.

Haworth has shown that the properties of the monosaccharides are best represented by regarding them as derivatives of the cyclic compounds *pyran* and *furan*. Thus the monosaccharides which normally occur



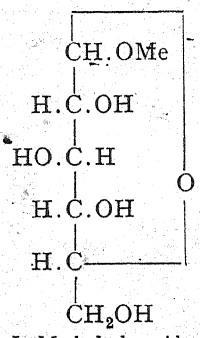


with an amylene oxide ring are now described as belonging to the **pyranose type,** *e.g. glucopyranose* (see formulæ VI and VII, p. 302). On the other hand, the labile γ-sugars are of the **furanose type,** examples of this class being the above-mentioned tetramethyl glucofuranose (tetramethyl γ-glucose) and fructose, which exists as fructopyranose in the free state but occurs as fructofuranose in derivatives such as cane sugar (p. 312) and inulin (p. 320). These formulæ also illustrate the ease with which the side-chain (CH_2OH) in glucose is oxidised to the carboxyl group, yielding glucuronic acid.

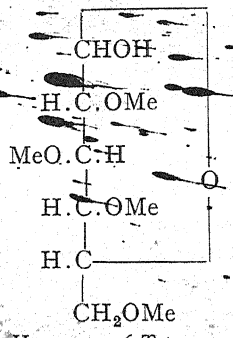
In formulæ such as VI the usual convention holds as to the disposition

[1] For further details see Haworth, *The Constitution of Sugars*; also Charlton, Haworth and Peat, *J. C. S.*, **1926**, 89; Haworth, Hirst and Miller, *ibid.*, **1927**, 2436; Hirst, *ibid.*, **1926**, 350.

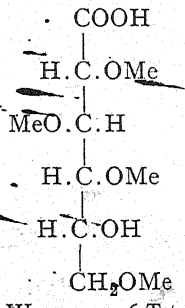
of the CHOH groups, a *d*-configuration being written with H on the left-hand side. When these conventional formulæ are built up in model form, the necessity of bringing the bond joining C_5 (marked by *) to O



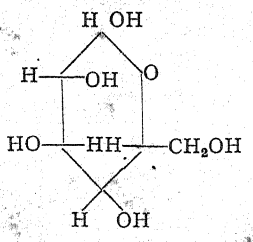
I. Methyl glucosides



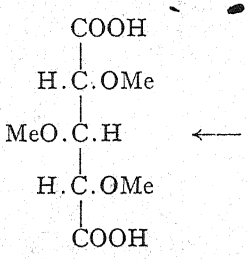
II. 2:3:4:6-Tetramethyl glucose



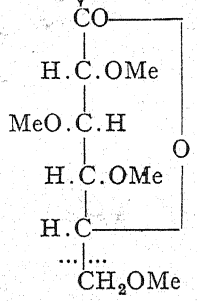
III. 2:3:4:6-Tetramethyl gluconic acid



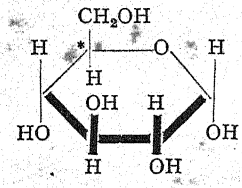
VI. *d*-Glucose (α or β)



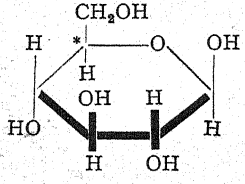
V. Xylo-trimethoxy-glutaric acid



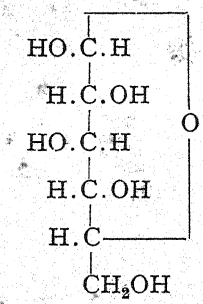
IV. Tetramethyl δ-gluconolactone



VII. α-Glucose (in perspective)



VIII. β-Glucose (in perspective)

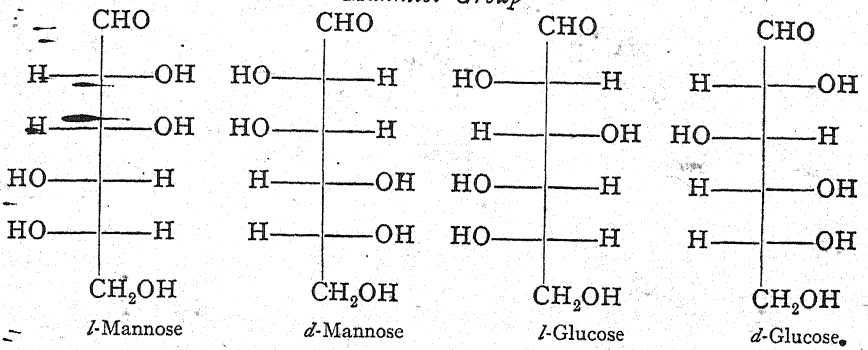


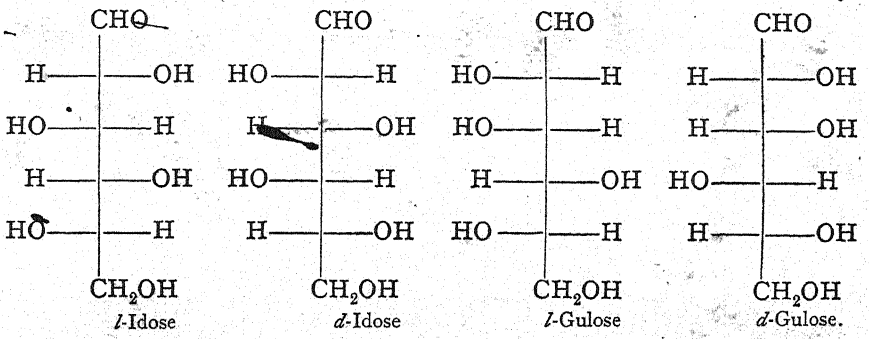
IX. β-Glucose.

into the same plane as the other C-atoms of the ring is found to cause an apparent displacement of the groups around C_5 (VII and VIII). This change is readily observed on converting the open-chain aldehydic model into the ring structure.

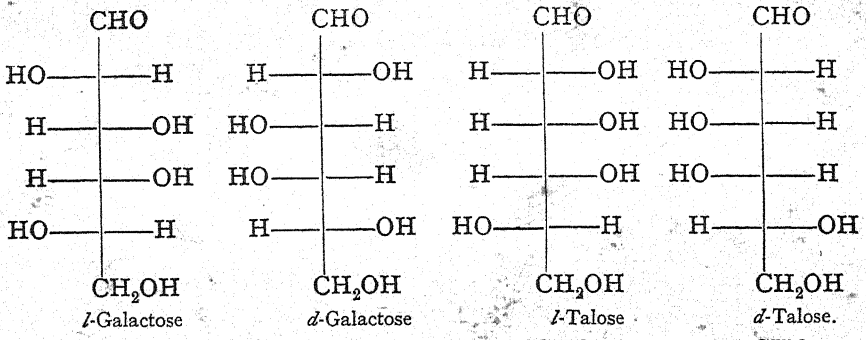
The Aldohexoses

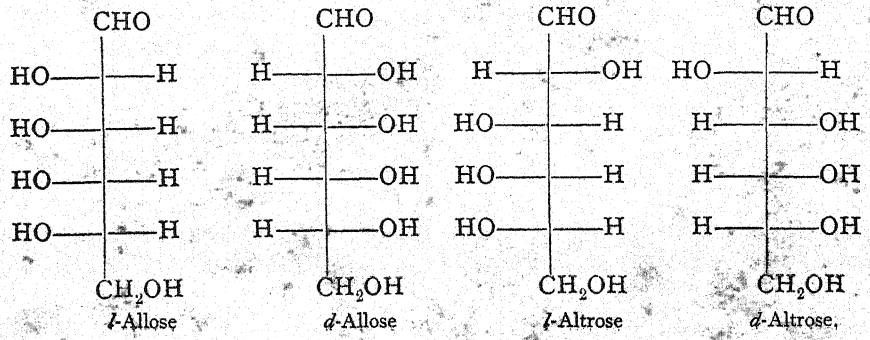
Mannitol Group





Dulcitol Group





The **ketohexoses** of the structural formula $CH_2OH.CHOH.CHOH.CHOH.CO.CH_2OH$, have only three asymmetric carbon atoms, indicating the possible existence of eight optically active forms. Like the aldohexoses, the ketohexoses occur normally in a pyranose form. *d*-Fructose is the most important member of this group.

In addition to the general properties of the hexoses quoted on p. 290, the following reactions are of interest.

When hexoses are treated in alcoholic solution with a little gaseous hydrochloric acid, glycosides or ethers are formed (p. 299).

When heated with moderately concentrated hydrochloric acid, hexoses yield *laevulinic acid* (p. 268) and in this respect differ from the pentoses. By isolating the acid as its silver salt the reaction can be used as a test for hexoses.

Like other carbohydrates, glucose condenses with one or more molecules of acetone, in the presence of a small amount of hydrogen chloride or zinc chloride. Water is eliminated and a crystalline cyclic acetal formed which contains the isopropylidene group $(CH_3)_2C:$, linked to two oxygen atoms of glucose. These *isopropylidene derivatives* are readily hydrolysed by mineral acids, but not by alkalis.

A test for ketoses is the evanescent red coloration formed when they are heated with resorcinol and 12½ per cent. hydrochloric acid.

An outstanding property of certain hexoses is their ability to undergo fermentation. As has been shown by E. Fischer,[1] this property is intimately connected with the spatial configuration of the sugar.

(a) *Aldohexoses*, $CH_2OH.(CHOH)_4.CHO$

***d*-Glucose,** *grape sugar*, *dextrose*, melts in the anhydrous state at 146°, the hydrated form ($1H_2O$) melting at 86°. It is found together with fructose in grapes, figs, and other sweet fruit, and also in honey. In small quantities it occurs in certain animal products, *e.g.* the urine of diabetic patients. Glucose and fructose are the only hexoses which occur in the free state.

Glucose is also formed by the hydrolysis of the polysaccharides, cane sugar, starch, and cellulose, and is prepared industrially from starch by boiling it with dilute sulphuric acid. The commercial product consists of more or less pure glucose; it is largely used in the manufacture of sweets and in the wine industry.

A synthesis of d-*glucose* has been effected by E. Fischer in the following manner:

Glycerol, on oxidation and subsequent treatment with alkalis, yields α-acrose, identical with *dl*-fructose. On reduction with the aid of sodium amalgam this gives the corresponding alcohol *dl*-mannitol, which on

[1] Compare p. 148. Lack of space forbids any discussion of the interesting researches of Fischer in this connection. For details, reference should be made to *Z. physiol. Ch.*, 1898, **26**, 60; see also Armstrong, *The Simple Carbohydrates and the Glycosides* (Longmans, Green).

oxidation is converted first into *dl*-mannose, and then into *dl*-mannonic acid. By recrystallising the strychnine salts of this acid it may be resolved into its *d*- and *l*- forms. When *d*-mannonic acid is heated with pyridine it is partially transformed by epimerisation (p. 294) into the stereoisomeric *d*-gluconic acid, the lactone of which on reduction with sodium amalgam finally yields *d*-glucose.

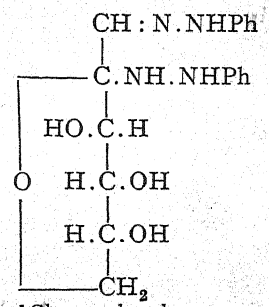
According to the conditions of crystallisation, glucose may be obtained anhydrous or combined with one molecule of water. Its aqueous solution is dextrorotatory and exhibits mutarotation, a freshly prepared solution rotating the plane of polarisation about twice as strongly as one which has been kept for some time or heated for a few minutes to the boiling-point. The final value is $[\alpha]_D = +52{\cdot}5°$.

α-Glucose ($[\alpha]_D + 110°$) may be prepared by allowing glucose to crystallise at ordinary temperatures from acetic acid containing a little water. Crystallisation from pyridine or at higher temperatures from pure acetic acid [1] yields **β-glucose** ($[\alpha]_D + 17{\cdot}5°$). Ordinary glucose is chiefly the α-compound.

Glucose undergoes the general reactions of aldoses described above. On oxidation it first yields d-*gluconic* acid, $CH_2OH(CHOH)_4COOH$, and finally d-*saccharic* acid, $COOH(CHOH)_4COOH$. On reduction it is transformed into the hexahydric alcohol, d-*sorbitol*, $CH_2OH(CHOH)_4CH_2OH$.

d-**Glucose-phenylosazone** is an intermediate in the conversion of *d*-glucose into *d*-fructose (see p. 292). It is sparingly soluble in water, from which it crystallises in yellow needles, m.p. 204° to 205°.

Glucosazone, like galactosazone, is known to undergo mutarotation in solution. It has recently been shown [2] that this is due to the presence of a 2 : 6-oxide ring in each of the above osazone structures.

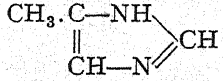


d-Glucose-phenylosazone.

It has already been mentioned that grape sugar is readily fermented, the main products of the action being alcohol and carbon dioxide.

Under the influence of dilute alkalis it suffers a series of changes and decompositions, which lead to the formation of hydroxy acids, such as lactic acid. On electrolytic oxidation at a lead anode it breaks up into formaldehyde and a pentose.[3]

When treated with ammonia in the form of ammoniacal zinc hydroxide, glucose is converted, even at the ordinary temperature, into methyl-iminazole (methyl glyoxaline).



[1] Behrend, *Ann.*, 1907, **353**, 106; Hudson and Dale, *J. A. C. S.*, 1917, **39**, 320. [2] E. E. Percival and E. G. V. Percival, *J. C. S.*, 1935, 1398; E. G. V. Percival, *ibid.*, 1938, 1385. [3] W. Löb and Pulvermacher, *Biochem. Zeitschr.*, 1909, **17**, 343.

d-**Glucosamine,** *chitosamine*, $CH_2OH.(CHOH)_3.CHNH_2.CHO$, is of special interest, as it stands midway between glucose and the α-amino acids, and thus forms a link between the carbohydrates and the proteins. It was first prepared from lobster shell by boiling the polysaccharide chitin contained therein with hydrochloric acid.[1] Glucosamine and other hexosamines are formed from mucins, the constituents of animal mucus, and from other proteins by hydrolysis with acids. The relationship of glucosamine to grape sugar is shown by its conversion into phenyl-glucosazone on treatment with phenyl-hydrazine.

d-Glucosamine has been synthesised by Fischer and Leuchs [2] in the following manner: *d*-arabinose, by treatment with ammonia, was converted into *d*-arabinosimine, which with hydrogen cyanide gave *d*-glucosaminic acid, $CH_2OH.(CHOH)_3.CH(NH_2).COOH$. The lactone of this acid was then reduced to *d*-glucosamine by means of sodium amalgam.

d-**Glucuronic acid,** $HOOC.(CHOH)_4.CHO$, is obtained by reducing the lactone of saccharic acid, $HOOC.(CHOH)_4.COOH$. It occurs in urine, either united with phenols in compounds of an ether type or with aromatic carboxy acids in the form of esters. In this way the phenols resulting, for example, from intestinal putrefaction are rendered harmless to the body. This protective function of glucuronic acid is also exerted by sulphuric acid and glycocoll. Glucuronic acid does not crystallise, and in this respect differs from its lactone, glucurone.

l-**Glucose** is formed in the same manner as *d*-glucose by reducing the lactone of *l*-gluconic acid. Similarly, *dl*-**glucose** can be obtained from *dl*-gluconic acid. *l*-Glucose forms crystals of melting-point 141°, but *dl*-glucose is a syrup.

d-**Mannose** is produced by careful oxidation of the hexahydric alcohol mannitol, which is present in various plants, or by boiling the polysaccharide seminine,[3] occurring in the shell of the ivory nut, with dilute sulphuric acid. Synthetically, it is obtained by reducing *d*-mannonic acid with sodium amalgam. It is a white hygroscopic compound of lower rotatory power than *d*-glucose, from which it differs only in the relative arrangement of the groups attached to the carbon atom adjacent to the aldehyde group (see p. 303). From this it follows that *d*-mannose and *d*-glucose yield the same osazone.

Oxidation converts *d*-mannose first into d-*mannonic acid*, $CH_2OH.(CHOH)_4.COOH$, and then into d-*mannosaccharic acid*, $COOH.(CHOH)_4.COOH$. It can be fermented with yeast.

The conversion of *d*-mannose into *d*-glucose may be effected through the intermediate formation of *d*-mannonic acid.

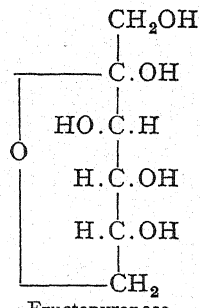
l-**Mannose** has been prepared from *l*-arabinose by the cyanhydrin synthesis and is laevorotatory. It unites with *d*-mannose to give **inactive mannose,** which is also formed by oxidation of the *dl*-mannitol obtained by reducing *dl*-fructose.

[1] Chitin, $C_{32}H_{54}O_{21}N_4$, forms the main skeletal tissue of the Insecta and Crustacea. It is closely related to N-acetyl-glucosamine. T. R. Offer, *Biochem. Zeitschr.*, 1907, **7**, 117. K. H. Meyer, *Zeit. für. ang. Chem.*, 1928, **41**, 941; *Ber.*, 1928, **61**, 1936. [2] *Ber.*, 1903, **36**, 24. P. M. Horton, *J. Indus. and Eng. Chem.*, 1921, **13**, 1040.

d-**Galactose** occurs in the ivy.[1] It is formed together with *d*-glucose by the hydrolysis of milk sugar, and also of *galactitol*, $C_9H_{18}O_7$, a substance present in the yellow lupin. It melts at 168°, is dextrorotatory, exhibits mutarotation and may be fermented. On reduction it yields *i-dulcitol* (p. 253), and on oxidation gives first *galactonic acid*, $CH_2OH.(CHOH)_4.COOH$, and then *mucic acid*, $COOH.(CHOH)_4.COOH$.

(b) *Ketohexoses*, $CH_2OH.(CHOH)_3.CO.CH_2OH$

d(—)**Fructose**, *fructopyranose*, also known as fruit sugar or lævulose, melts at 95° and is found with *d*-glucose in honey and the juice of sweet fruits. The hydrolysis of cane sugar leads to the production of equimolecular amounts of *d*-fructose and *d*-glucose. On the other hand, inulin, a polysaccharide occurring in the roots of the dahlia, chicory and many *Compositæ*, yields *d*-fructose alone. From the latter sources it is prepared industrially.



Fructopyranose.

The osazone of fructose is formed very readily, even in the cold, and is identical with *d*-glucosazone (compare configurational formulæ of fructose and glucose). The *conversion of glucose into fructose* by way of the osazone has already been described on p. 293. In consequence of its spatial relationship to *d*-glucose, fruit sugar is known as *d*-fructose, although it has a laevorotation of $[\alpha]_D = -92°$. As represented above, fructose normally exists in the form of fructopyranose, with a 1:5-oxidic ring. In the combined state, however, the fructose residue contains a 1:4-ring and is thus of the fructofuranose type (see cane sugar).

Fructose is more soluble in water than glucose, and is readily fermented, when it gives the same products as grape sugar. On reduction it is converted into a mixture of *d*-mannitol and *d*-sorbitol. On oxidation it breaks up into *d*-erythronic acid, $CH_2OH.(CHOH)_2.COOH$, and glycollic acid, $CH_2OH.COOH$.

Interconversion of d-*Glucose*, d-*Fructose and* d-*Mannose*[2]

As was first shown by Lobry de Bruyn, any one of the above three hexoses, under the influence of hydroxyl ions (very dilute alkalis or alkaline earths, sodium acetate, ammonia, etc.), is converted into a mixture of all three sugars in equilibrium with one another, as indicated in the following scheme:

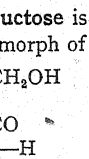
Glucose ⇌ Fructose ⇌ Mannose.

d-Fructose appears to be formed as an intermediate in the above changes. This is strongly supported by the fact that mannose, of $[\alpha]_D = +14°$, yields with dilute alkalis a strongly laevorotatory mixture (owing to the

[1] v. Lippmann, *Ber.*, 1910, **43**, 3611. [2] Lobry de Bruyn and A. van Ekenstein, *Ber.*, 1895, **28**, 3078.

formation of fructose), the rotation subsequently swinging back towards zero as the proportion of glucose increases.

l-**Fructose** is produced by the fermentation of racemic fructose. It is the optical enantiomorph of the laevorotatory *d*-fructose, and is therefore dextrorotatory.


l-Sorbose.

dl-**Fructose,** or **α-Acrose,** is the resolvable inactive form produced synthetically from glycerose or formaldehyde, and has played a most important part in the synthesis of sugars.

l-**Sorbose,** *sorbinose,* m.p. 154°, is a ketose obtained from the juice of mountain-ash berries. These contain the alcohol *d*-sorbitol, which is converted into sorbose by the action of an oxidising organism, *Bacterium xylinum.* *l*-Sorbose is now produced in quantity from the sorbitol prepared by catalytic hydrogenation of *d*-glucose. It is not fermented by yeast.

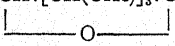
Glycosides [1]

In close relationship to the monosaccharides are the glycosides, which are found very widely distributed in the vegetable kingdom. They may be considered as derivatives of the ether type formed by combination of a sugar (commonly glucose) with one or more other substances. Well-known representatives of this class are *amygdalin,* a constituent of bitter almonds; *salicin,* which was used as a febrifuge by the older school of medicine; *indican*; *ruberythric acid.* Under the influence of enzymes, or on being heated with dilute acids or alkalis, a glycoside breaks down into a sugar (or mixture of sugars) and the compound with which it was originally united. The sugar-free compound is known as an *aglucone* or *aglycone.*

Glycosides of the simplest type have been synthesised by E. Fischer,[2] by bringing a sugar, *e.g.* glucose, into reaction with an alcohol in the presence of hydrochloric acid.

$$C_6H_{12}O_6 + CH_3OH = C_6H_{11}O_5.OCH_3 + H_2O.$$

Another compound of similar structure, which has come into use in the synthesis of glycosides and other sugar derivatives, is *aceto-bromo-glucose,*[3] prepared from penta-acetyl-glucose by treatment with hydrobromic acid.



As is shown by the inactivity of these compounds towards phenyl-hydrazine, they no longer contain a free aldehyde group. The latter must therefore be united to the alcohol in the same manner as in the acetals (see p. 178). For the isomerism of α- and β- glucosides and a means of distinguishing between these two forms by enzyme action, see p. 299 *et seq.*

A detailed investigation of the simpler artificial glycosides led Fischer to the discovery that there was no fundamental difference between the glycosides and the polysaccharides. The latter are glycosides of the monosaccharides themselves.

Linamarin, the glucoside of acetone-cyanhydrin, $C_6H_{11}O_5.O.C(CH_3)_2.CN$, was first isolated from the seeds and embryo of flax. It forms colourless needles, m.p. 134°, possessing a fresh bitter taste. On hydrolysis with dilute acids it decomposes into glucose, hydrogen cyanide, and acetone. It has also been prepared synthetically.[4]

4. Heptoses, Octoses and Nonoses

By means of the cyanhydrin synthesis described on p. 294, it is possible to convert an aldohexose by successive stages into the corresponding heptose, octose and nonose. Of these it need only be mentioned that the heptoses and octoses are not fermentable, whereas *d*-manno-nonose ferments with yeast.

[2] See E. F. Armstrong, *The Simple Carbohydrates and the Glycosides* (Longmans, Green). [2] E. Fischer, *Ber.*, 1893, **26**, 2400; 1895, **28**, 1145; 1909, **42**, 1465. [3] Compare *Ber.*, 1920, **53**, 440, 2150; 1921, **54**, 499; 1922, **55**, 929. [4] *Ber.*, 1919, **52**, 854.

II.—DISACCHARIDES, $C_{12}H_{22}O_{11}$

Unlike the higher polysaccharides, the di- and trisaccharides still retain the sweetness of taste characteristic of monosaccharides.

Until recently the only disaccharides known were derived from the hexoses, $C_6H_{12}O_6$, and therefore possessed the formula $C_{12}H_{22}O_{11}$. On hydrolysis these take up water and are decomposed into two hexose molecules, $C_{12}H_{22}O_{11}+H_2O=2C_6H_{12}O_6$. This change may be effected by boiling with dilute acids, or by the action of enzymes such as diastase, emulsin and invertase. All disaccharides yield glucose as one of the hydrolytic products, the other may also be glucose (as in the case of maltose), fructose (from cane sugar), or galactose (from milk sugar).

Disaccharides have now been found in plants which give on hydrolysis 1 mol. hexose and 1 mol. pentose, *e.g. vicianose* (*Bertrand*) an arabinosido-glucose, and *primverose*, a xylosido-glucose. Both of these disaccharides have been synthesised by Helferich.[1]

The ease with which disaccharides are hydrolysed supports the view that they are ethereal anhydrides of hexoses, the link joining the two hexose molecules being supplied by the oxygen of an alcoholic, aldehydic or ketonic group. If union occurs in such a way that the reducing group of one of the hexose constituents is left intact, then the disaccharides so formed (*e.g.* lactose and maltose) will still exhibit the reactions of aldoses. They will reduce Fehling's solution and give osazones with phenyl-hydrazine. On the other hand, cane sugar shows none of these reactions, and in it the reducing groups of both glucose and fructose appear to be bound.

In determining the constitution of di- and polysaccharides the chief difficulty lies in deciding the exact position of the oxygen linkings taking part in anhydride formation, and the particular stereoisomeric forms of the monosaccharides present. Some information on these points is afforded by a study of enzyme action.

In recent years this problem has been attacked systematically on lines developed by Purdie, Irvine, Haworth and others. The method adopted involves, in the first instance, the preparation of a large number of partially or completely methylated aldoses and ketoses.[2] The polysaccharide under investigation is then fully methylated [3] and submitted to careful hydrolysis or other chemical change, *e.g.* oxidation. From an examination of the simpler methylated derivatives so obtained it is possible to determine the structure of the parent compound.[4]

Cane Sugar, *sucrose*, *saccharose*, m.p. 160°, occurs in the juice of the

[1] B. Helferich and co-workers, *Ann.*, 1927, **455**, 168; 1928, **465**, 166. [2] Irvine and co-workers, *J. C. S.*, 1913, **103**, 564, 575; 1916, **109**, 1305; 1922, **121**, 2696. For a detailed description of the methods employed see *Some Constitutional Problems of Carbohydrate Chemistry*, Irvine, *J. C. S.*, 1922, **123**, 898; *The Constitution of Sugars*, W. N. Haworth. [3] For the use of methyl sulphate in this connection see W. N. Haworth, *J. C. S.*, 1915, **107**, 8. [4] Irvine, Steel and Shannon, *J. C. S.*, 1922, **121**, 1060; Haworth and Leitch, *J. C. S.*, 1918, **113**, 188; 1919, **115**, 809.

sugar cane, sugar beet, sugar maple, maize, and many other plants. The first two sources in particular are utilised in the preparation of sugar on the large scale.

Technical Preparation of Sugar from Beets.—The beets are sliced into thin sections by mechanical means, and the sugar is extracted by a *diffusion process* involving systematic treatment with water.[1] The water is first admitted to a " diffuser " containing the almost completely extracted roots, and after remaining there for a few minutes is transferred to the next in the series, finally coming into contact with fresh roots. The extracted roots are expressed and utilised as fodder, after being dried to keep them in good condition.

The subsequent *processes for purifying the juice* have as their aim the removal of the majority of other organic substances present, which would otherwise hinder the crystallisation of the sugar. For this purpose the extract is treated at a moderate temperature with milk of lime, by which means oxalic acid, citric acid, and phosphates are precipitated, other acids are neutralised or, like asparagine, decomposed, and most of the protein and colouring matter is thrown out of solution. The necessity of using an excess of lime leads to the formation of insoluble calcium sucrate ; this is decomposed by passing in carbon dioxide, when calcium is precipitated as calcium carbonate. Sulphur dioxide is frequently used in place of carbon dioxide, and yields an extract of better colour.

In order to avoid decomposition the *evaporation of the purified extract* is conducted in vacuum pans, and is continued until a concentration is reached at which crystallisation sets in. Finally, the masses of crystals are broken up and the mother liquor removed by centrifuging. The moist crystals remaining in the centrifuge constitute the *raw sugar* of commerce, and the dark brown fluid which is run off is known as *molasses*.

Raw sugar is refined by bringing it into solution, treating with milk of lime, and filtering through " activated " charcoal. After several repetitions of this process the liquid is concentrated in vacuum pans until crystallisation sets in. The refined sugar so obtained contains 99·9 per cent. saccharose.

Recovery of Molasses.—Molasses contains about 20 per cent. water and 50 per cent. sugar. The latter, however, is only in part recoverable by further concentration of the molasses, as it is held in solution by the presence of impurities. It is therefore necessary to separate the sugar from the residual matter by special treatment, for which purpose a large number of processes are available.

(*a*) *The Osmotic Process* consists in dialysing the molasses through parchment paper, when inorganic salts are the first to diffuse out of the mixture, followed by salts of organic acids and sugar, and finally sugar alone. Albuminous substances which had previously hindered crystallisa-

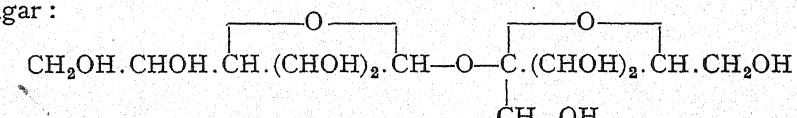
[1] Methods are also under investigation by which the sliced beets are dried and stored. This allows the extraction process to be operated throughout the year, independently of the seasonal supply of raw material.

tion, being colloidal in nature, are unable to pass through the membrane. The diffused liquid is worked up for sugar by evaporation *in vacuo*, and the albuminous residue, which still contains a certain amount of sugar, is used as a fertiliser.

(*b*) Separation by means of *strontium* or *calcium sucrates*. This process depends on the property which sugar possesses of giving insoluble or sparingly soluble sucrates with lime or strontium hydroxide, *e.g.* *tricalcium sucrate*, $C_{12}H_{22}O_{11}$, $3CaO$, *distrontium sucrate*, $C_{12}H_{22}O_{11}$, $2SrO$. When the diluted molasses is treated with either of the above hydroxides a precipitate of the corresponding sucrate is thrown out of solution. Inorganic and organic impurities in the molasses remain dissolved and are removed in a filter press. After washing the sucrates with a little water or aqueous alcohol they are decomposed with carbon dioxide, and the sugar solution so obtained is evaporated as before in vacuum pans.

Properties of Cane Sugar.—Cane sugar crystallises in clear monoclinic prisms, which are very sparingly soluble in alcohol, but dissolve easily in water to give a solution rotating the plane of polarisation to the right. Cane sugar melts at 160° and on cooling solidifies to a vitreous mass (*barley sugar*), which gradually reverts to the crystalline state. On stronger heating it forms a brown product known as *caramel*, a mixture of decomposition products of sugar used for tinting liqueurs and confectionery. As has already been mentioned above, it forms sucrates with bases. When warmed with dilute acids it is rapidly hydrolysed to a mixture of glucose and fructose. Glucose resembles cane sugar in being a dextrorotatory compound, but fructose is so strongly laevorotatory that the equimolecular mixture of glucose and fructose obtained by hydrolysis rotates the plane of polarisation to the left. For this reason the above process is known as the *inversion of cane sugar*, and the mixture of *d*-glucose and *d*-fructose so obtained is called *invert sugar*. The latter usually forms a syrup, which is sweeter than cane sugar and is used as a substitute for honey, for improving wine musts, and in the preparation of champagne, liqueurs and fruit preserves.

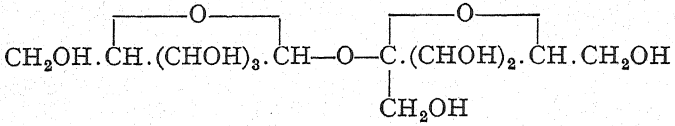
Cane sugar no longer gives the reactions of the monosaccharides, *e.g.* it forms no osazone and does not reduce Fehling's solution. On heating with acetic anhydride it yields an octa-acetyl derivative. Working from these data E. Fischer suggested the following formula for cane sugar :



Later work on the oxidation of octamethyl-sucrose and its hydrolysis products,[1] however, points to the glucose residue possessing a pyranose

[1] Avery, Haworth and Hirst, *J. C. S.*, 1927, 2308; Haworth, Hirst and Nicholson, *ibid.*, 1513; Haworth, Hirst and Learner, *ibid.*, 2432.

structure in place of the furanose structure given above, leading to the formula

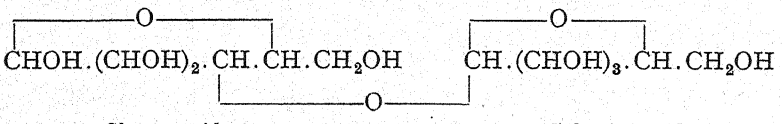


Glucose residue Fructose residue.

It may be noted that the fructose residue in this case possesses the labile 1 : 4- and not the normal 1 : 5-oxidic ring, and that the aldehydic and ketonic groups of glucose and fructose have both been masked by anhydride formation.[1]

Milk Sugar, *lactose*, *lactobiose*, is found almost exclusively in the milk of mammals. It is prepared industrially from whey, obtained as a by-product in the manufacture of cheese from milk. The whey is evaporated in vacuum pans until crystallisation sets in, and the crude milk sugar so obtained is purified by recrystallisation from water with the addition of animal charcoal.

It forms hard rhombic crystals containing one molecule of water, which become anhydrous at 140° and then melt with decomposition at 205°. It is dextrorotatory and undergoes mutarotation. On hydrolysis it decomposes into *d*-galactose and *d*-glucose. Lactose forms an osazone and reduces Fehling's solution. The carbonyl group present in the molecule is that corresponding to *d*-glucose, since lactose, on oxidation with bromine water, yields lactobionic acid, which on hydrolysis breaks up into *d*-galactose and *d*-gluconic acid. These facts, together with the results of a recent examination of the behaviour of the completely methylated sugar on hydrolysis,[2] point to the following formula for lactose :



Glucose residue Galactose residue.

Lactose is not as sweet as cane sugar. It is used in medicine, in the silvering of mirrors, and is frequently added to milk intended for infant consumption. It is not easily fermented with yeast but readily undergoes lactic acid fermentation. Alcoholic fermentation may also be induced by means of kefir grains. *Koumiss* is a Russian beverage made in a similar way by fermenting mare's milk.

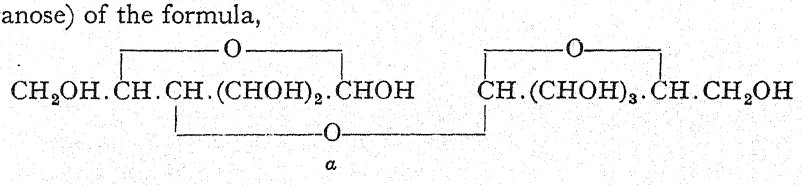
Malt Sugar, *maltose*, maltobiose, is produced by the action of diastase on starch (see p. 147) and is an intermediate product in the preparation of alcohol and alcoholic liquors.

In the *technical preparation of maltose* starch is mixed to a paste

[1] A. Pictet and Vogel (*Helv. Chim. Acta*, 1928, **11**, 436) claimed to have effected a synthesis of cane sugar, but later investigators have failed to confirm this work. Compare Georg, *Helv. Chim. Acta*, 1933, **16**, 130. Irvine and Stiller, *J. C. S.*, A., 1932, 500. Pictet, *Helv. Chim. Acta*, 1933, **16**, 144. [2] Haworth, Loach and Long, *J. C. S.*, **1927**, 3150.

with a sufficient quantity of water and the addition of 1 to 3 per cent. of green malt (see p. 147), the temperature of the fluid being kept below 70°. It is then cooled to 55°, a further 4 to 7 per cent. of green malt added and the mixture maintained at this temperature till all the starch is decomposed. The solution of malt sugar is boiled in order to coagulate dissolved protein, and insoluble matter is filtered off to be used as cattle food. The concentrated liquid may be used to prepare crystalline maltose, or may be placed on the market as *malt syrup* or *malt extract.*

Maltose crystallises from water in small needles (1 mol. H_2O), which melt at 100° when rapidly heated. It is strongly dextrorotatory, and on hydrolysis with dilute acids yields *d*-glucose alone. It gives the same reactions as the monosaccharides, reducing Fehling's solution and forming an osazone. In these respects maltose resembles lactose. It can be oxidised to maltobionic acid, which contains the same number of carbon atoms and is monobasic. The latter on hydrolysis yields *d*-gluconic acid. Hence it may be concluded that maltose is composed of two molecules of glucose united in such a way that the aldehyde group of the one remains intact, while that of the other has entered into anhydride formation.[1] It is represented as a glucose-α-glucoside (α-glucopyranosido-glucopyranose) of the formula,



Trisaccharides, $C_{18}H_{32}O_{16}$

Few examples of this group of polysaccharides have been discovered, the best known representative being **raffinose,** *melitose* or *melitriose,* which forms the chief constituent of Australian manna. It also occurs in beetroot, and is consequently found in beet molasses. Raffinose crystallises in fine needles with five molecules of water of crystallisation, which are driven off at 120°. On hydrolysis it takes up two molecules of water, yielding an equimolecular mixture of *d*-fructose, *d*-glucose, and galactose. Raffinose shows none of the reactions of the monosaccharides, and we must therefore assume that it is built up from the above three sugars in such a manner that all three carbonyl groups are modified by intramolecular linkage.

III.—HIGHER POLYSACCHARIDES $(C_6H_{10}O_5)_n$

As has already been stated on p. 289, the formula of these compounds is usually expressed as $(C_6H_{10}O_5)_n$. It was shown by Kiliani [2] that this is not a correct representation of their composition. Properly speaking, the formula is $(C_6H_{10}O_5)_n$, H_2O or $C_{6n}H_{10n+2}O_{5n+1}$, in which the value of n is not known with certainty. The majority of the polysaccharides are amorphous, tasteless compounds, some of which are insoluble in water. When hydrolysed by boiling with dilute acids, or by treatment

[1] For the structure of maltose see Haworth and Peat, *J. C. S.*, **1926**, 3094. [2] Kiliani, *Ch. Zeit.*, 1908, **32**, 366.

with enzymes, they are all converted into monosaccharides, which may be either hexoses or pentoses. The polysaccharides are therefore considered to be built up from hexoses and pentoses by means of oxygen linkings, in the same manner as the di- and trisaccharides. The presence of hydroxyl groups is shown by their property of forming acetyl derivatives and nitric esters.

Polysaccharides are found widely distributed in the plant and animal kingdoms. But whereas in the animal organism only two polysaccharides, *glycogen* and *cellulose*,[1] have so far been discovered, the number in the plant world is very great. In the latter source they function not only as a storehouse of carbohydrate food, but also form the chief constituents of cell membrane and supporting tissue; in the animal organism these parts are composed mainly of proteins. Polysaccharides of animal origin are built up of glucose alone; those from vegetable sources may yield in addition other monosaccharides on hydrolysis.

Starch, *amylum*, occurs very widely distributed in the vegetable kingdom. Among the raw products used industrially in the preparation of starch may be mentioned the grain or fruit of wheat, maize, rice and horse-chestnut, the tubers of the potato and the pith of the sago palm. In these the starch is stored as granules, which vary in form and size according to the nature of the plant. Under the microscope the grains may be seen to consist of an inner nucleus, around which are deposited concentric layers. The starch granules are not homogeneous but contain two very similar polysaccharides, namely **amylose,**[2] a water-soluble component occurring in the interior of the cells, and **amylopectin,** a compound insoluble in cold water and present in the cell walls. (For further details see pp. 316-319.)

Starch is a white hygroscopic powder, with neither taste nor smell. It is insoluble in cold water, but in hot water it forms a paste which rotates the plane of polarisation to the right. This paste-forming property is due to the presence of amylopectin. In addition to carbohydrate both amylose and amylopectin contain a small amount of combined phosphoric acid, which varies in amount with the origin of the starch but in general does not exceed 0·2 per cent. (calculated as P_2O_5).

A peculiarity of starch is the blue colour it yields with iodine in the presence of a little potassium iodide or hydriodic acid. This is a very sensitive test. The colour appears to be due to the adsorption of iodine on the surface of the starch, and not to the formation of a definite compound. When boiled with dilute acid, starch is first transformed into a soluble gummy mixture of products known as *dextrin*, and finally into *d*-glucose. Under suitable conditions the conversion is quantitative. Starch also hydrolyses under the influence of certain enzymes, known

[1] *Tunicin*, an "animal cellulose," occurs in the mantle or leathery skin of the tunicata, found in shallow sea-water. [2] Amylose is conveniently isolated by freezing starch paste at −10° to −15°, subsequently extracting with water at 50° to 60° and precipitating the extract with alcohol (A. R. Ling and D. R. Nanji, *J. C. S.*, 1923, 2673).

as *diastases* or *amylases* (see p. 147), giving in this case a nearly quantitative yield of maltose. This reaction is of great importance in the industrial preparation of alcohol. **Dextrin** is manufactured by heating starch alone, or in the presence of a little nitric acid, to 110°, and is used as a mucilage under the name of " British gum." Concentrated nitric acid dissolves starch with the formation of nitric esters.

The starch molecule contains no free carbonyl group, since it yields no compound with phenyl-hydrazine and does not reduce Fehling's solution.

As has already been emphasised, starch is one of the most valuable constituents of food, and also forms the basis of the brewing industry and the manufacture of dextrin. It is employed in laundry work as a stiffening and for giving a finish to textiles, as an adhesive (starch paste), as a thickening agent for colours in calico printing, and for sizing paper.

Technical Preparation of Starch.—The following description gives details of the manufacture of starch from potatoes. From other sources it is obtained in a similar manner. The starch granules are enclosed comparatively loosely in the cells of the potato, and the process of manufacture consists in rupturing the cell walls and washing the starch grains free from cellulose. After being treated in a washing machine, the potatoes are disintegrated, yielding a paste consisting of starch granules, finely divided fibrous tissue, and an aqueous solution containing the juices of the potato. This mixture is washed with water in a sifting machine. The pulp remaining on the sieves is used as fodder, and the suspension of fibrous matter and starch granules which passes through is allowed to stand for a time, when the specifically heavier starch separates out. A little fibrous matter is also carried down by the last layers deposited. The starch pulp so obtained is carefully washed, centrifuged, and slowly dried, when it is ready for the market. It still contains about 16 to 18 per cent. water.

Lichenin, *lichen starch*, occurs in many lichens, *e.g.* Iceland moss. On hydrolysis with acids it yields *d*-glucose.

Glycogen, animal starch or *liver starch* occurs in the animal organism,[1] where, like starch in the vegetable kingdom, it functions as a carbohydrate reserve. It can be isolated from liver as a white amorphous powder, but is also present in muscular tissue and in other parts of the organism. During muscular effort the glycogen content of the muscle diminishes, owing to its conversion into lactic acid. This change occurs through the intermediate formation of *lactacidogen*, a sugar containing combined phosphoric acid. On hydrolysis with acids or ferments it finally yields *d*-glucose. Glycogen differs from starch in dissolving to an opalescent solution in cold water, and in giving with iodine a reddish-brown coloration. It is very stable towards hot alkalis, and is precipitated with alcohol. All preparations of glycogen appear to exhibit weak reducing powers towards Fehling's solution (see below).

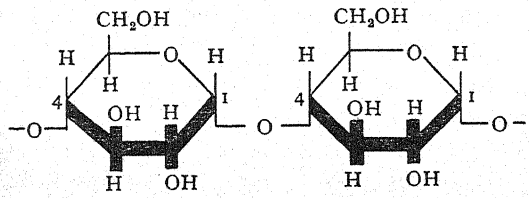
Inulin is a polysaccharide found in the roots of the dahlia, chicory and various *Compositæ*. It is coloured yellow by iodine, and on hydrolysis is converted quantitatively into *d*-fructose.

[1] An unusual case of the occurrence of glycogen in a plant source (the seed of sweet corn, *Zea Mays*) has recently been recorded by D. L. Morris and C. T. Morris, *J. Biol. Chem.*, 1939, **130**, 535, and W. Z. Hassid and R. M. McCready, *J. A. C. S.*, 1941, **63**, 1632.

Pectins are very complex gelatinising compounds which are found widely distributed in nature, especially in fruit juices. They are closely related to the carbohydrates. Pectins isolated from apple and from strawberry juice consist of chains of galacturonic acid residues linked through the 1:4-positions. Probably this structure is characteristic of the pectin group.

The Molecular Structure of Polysaccharides.[1] Starch, Glycogen and Inulin

Starch.—As in the case of the relatively simple di- and trisaccharides, valuable information concerning the structure of the complex polysaccharides has been obtained by examining the behaviour of the parent compounds and their methyl derivatives towards hydrolytic agents. Thus starch may be converted quantitatively into *d*-glucose by heating it with dilute mineral acid. Similarly, on treatment with diastase or amylase it forms maltose in 80 per cent. yield. In view of the known structure of maltose as a glucose-α-glucoside (p. 313), the possibility suggested itself that the starch molecule is built up of a series of α-glucose units joined through carbon atoms 1 and 4 by glycosidic links (compare



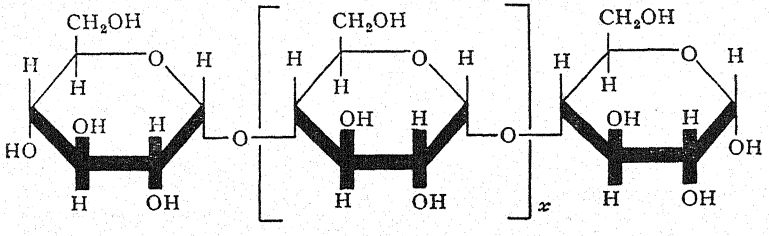
formula VII for α-glucose on p. 302). Definite support for this assumption was obtained later from investigations on methylation products of starch. Completely methylated starch (trimethyl starch) was found to give on hydrolysis an almost theoretical yield of 2:3:6-trimethyl glucose. This is seen to be in entire agreement with the above formula, in which only the hydroxyl groups in positions 2, 3 and 6 are open to attack by the methylating agent.

The fundamental unit of the molecular structure having been established with some degree of certainty, evidence was next sought which would enable an estimate to be made of the molecular weight of starch and throw some light upon the general arrangement of the molecule, which might be regarded as built up of α-glucose units linked together to form either an open chain or a closed loop. Furthermore, the starch granule is a mixture of the two components, amylose and amylopectin, the relationship between which is as yet not clearly understood.

Considerable progress has now been made towards a solution of these problems, mainly through the recent work of Haworth, Hirst and

[1] J. C. Irvine and J. Macdonald, *J. C. S.*, 1926, 1502; W. N. Haworth, E. L. Hirst and J. I. Webb, *J. C. S.*, 1928, 2683. See also Haworth, *Chemistry and Industry*, 1935, **54**, 859.

their collaborators.[1] A highly purified sample of fully methylated *amylose* was hydrolysed according to the latest procedure with methyl alcoholic hydrogen chloride, and the resulting products separated by fractional distillation in a high vacuum. It was found that admixed with a large amount of 2:3:6-trimethyl glucose was a small quantity of 2:3:4:6-tetramethyl glucose, each of these hydrolytic fragments being present in the form of its methyl glucoside as a result of further interaction with the hydrolysing medium. Now if the constituent monosaccharide units were originally joined together in a closed loop, only one type of methylated sugar should be formed when the loop is disrupted by hydrolysis. The production of two types, on the other hand, indicates that an open chain is present and that one of the terminal α-glucose residues is thus capable of becoming more highly methylated than the remaining units. This is illustrated in the following formula for starch, in which the terminal



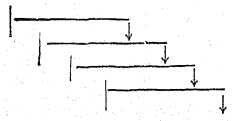
Amylose.

group on the left yields a molecule of tetramethyl glucose and the central portion x molecules of trimethyl glucose. The right-hand end group gives rise to the methyl glucoside of trimethyl glucose, but this indicates no differentiation from the central part of the molecule since, as has already been stated, under the conditions of experiment all the glucose residues are eventually isolated in the form of their methyl glucosides. From the proportion of tetramethyl glucose found it was estimated that each chain contained about 25 to 30 units of α-glucose, which leads to a molecular weight of approximately 5000 for amylose. Identical results were also obtained for methylated samples of *amylopectin*. Since no degradation appears to occur during the preparation of the methylated amylose, it is concluded that the molecule of starch is represented in all fundamental respects by the above formula. The same values are obtained for starches from a variety of biological sources.

The molecular weight of starch in the methylated or acetylated form has been deduced from the viscosity of solution (Staudinger's method), osmotic pressure and the rate of sedimentation in the ultracentrifuge. Values much greater than the 5000 corresponding to the above " chemical unit " were thus obtained, some of them of the order of 400,000, which suggested that these units are aggregated together by either chemical or physical forces to form a more complex pattern. Further information

[1] Haworth and Hirst, *Trans. Farad. Soc.*, 1933, **29**, 14. D. K. Baird, Haworth and Hirst, *J. C. S.*, 1935, 1201.

has been gained by the work of E. L. Hirst and G. T. Young,[1] who disaggregated methylated starches of high molecular weight by graded treatment with dilute methyl-alcoholic oxalic acid, and examined the fractions at intervals by end-group assay and physical molecular weight determinations. They found that the characteristic properties of starch, including the high optical rotation and lack of reducing power, were retained until the physical molecular weight had been diminished to about three times that of the chemical unit. At this stage the chain length as determined by end-group assay still approximated to 30 glucose residues. Later research [2] shows that starch is best represented by a laminated structure of the type shown in the diagram. Each repeating unit of 24-30 glucose residues is indicated by a straight line ending in an arrow head corresponding to the reducing group. Absence of reducing properties is accounted for by the reducing group being joined by a glycosidic link to the primary alcohol group (C_6) of a glucose unit in an adjacent chain. Evidence in support of this point is obtained by a further examination of the hydrolysis products from methylated starch. In addition to the main component, 2:3:6-trimethyl-glucose, this led to the isolation of 2:3-*dimethyl glucose* in about the same amount as tetramethyl glucose from the end group. As carbon atom C_4 is employed in linking together the units in the main chains, C_6 must be the position at which these chains are aggregated.



When the molecular model corresponding to the formula of starch is examined, it is seen that owing to the valency angles of the α-glucosidic links the spatial distribution of the monosaccharide units is not linear, but a twisted structure which would be expected to facilitate the aggregation and interlocking of the molecules. This fact may explain the characteristic physical differences shown by starch and cellulose, the latter being represented by long straight macro-molecules of a thread-like nature.

Synthetic Starch.—During the past few years it has been discovered that *glucose-1-phosphate* (α-glucopyranose-1-phosphoric acid) can undergo reversible transformation into a polysaccharide in the presence of *phosphorylases*, which are enzymes occurring in various animal and vegetable sources such as muscle, liver, yeast and potatoes. Cori, Kiessling and others, working principally with enzymes from animal tissues and from yeast, have concluded that glycogen [3] is formed *in vivo* from the glucose ester.

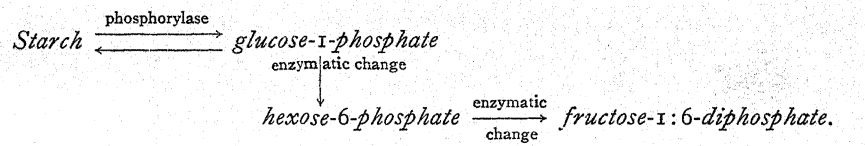
Glucose-1-phosphate $\rightleftharpoons$ *glycogen+free phosphate.*

Hanes,[4] using a purified phosphorylase from potato juice, has succeeded in converting glucose-1-phosphate in high yield into a starch, which strongly resembles natural starch and is still more closely identified with a less soluble fraction obtainable from the natural product. The

[1] *J. C. S.*, **1939**, 1471. [2] Barker, Hirst and Young, *Nature*, 1941, **147**, 296. [3] C. F. Cori and G. T. Cori, *Proc. Soc. Exptl. Biol. Med.*, 1936, **34**, 702; C. F. Cori, *J. Biol. Chem.*, 1940, **26**, 285. W. Kiessling, *Biochem. Z.*, 1939, **202**, 50. [4] C. S. Hanes, *Proc. Roy. Soc., Lond.*, 1940, **B128**, 421; **B129**, 174. Hanes suggests that the polysaccharide examined by the above workers may have been more closely related to a starch than to glycogen.

synthetic starch deposits in granular form and has a high rotation, $[\alpha]_D$ being about 200°. It gives a more intense blue with iodine than ordinary starch and is less soluble in water. From aqueous solutions it tends to deposit again, except when present in high dilution. Like certain other polysaccharides it dissolves in strong alkalis. With α-malt-amylase the synthetic starch undergoes hydrolysis in the same manner as natural starch, but with β-amylase (from germinating barley) it is completely hydrolysed, whereas the hydrolysis of natural starch ceases after 60% conversion. In these points of difference the synthetic product closely resembles the less soluble "amylo-amylose" fraction of whole natural starch, which behaves in the same way towards β-amylase and also tends to deposit from aqueous solution. Astbury, Bell and Hanes have carried out an X-ray examination and find that the patterns of the natural and synthetic starches are essentially the same.[1] Further investigations by end-group analysis are in progress.[2]

These discoveries have a fundamental bearing on the function of the reserve carbohydrates in plant and animal metabolism. Some mechanism apparently exists in the plant for the production of glucose-1-phosphate, which plays the part of a key compound, being not only the precursor of starch but also undergoing enzymatic changes by which it is converted into hexose-6-phosphate and fructose-1 : 6-diphosphate, and thence into smaller disruption products (compare fermentation of glucose).



In this respect, starch in the presence of phosphorylase and free phosphate may be regarded as a readily accessible reservoir of glucose-1-phosphate.

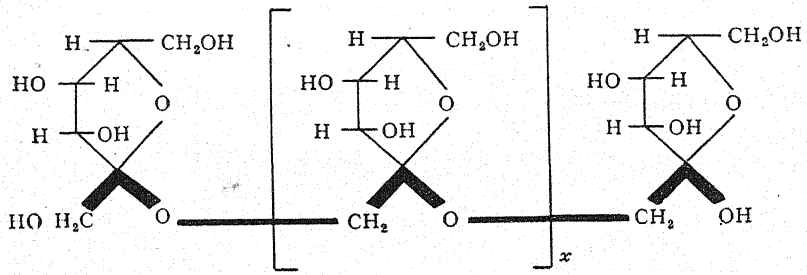
Glycogen.—The constitution of glycogen (p. 315) has been determined in a similar manner [3] to that of starch. This compound resembles starch in many of its chemical properties, being converted quantitatively into glucose on acid hydrolysis and forming maltose with diastatic ferments. The molecule thus consists of α-glucose units linked together in the same manner as in maltose. In this case, however, the molecule is smaller and the proportion of tetramethyl glucose obtained from methylated glycogen indicates that the chains only contain an average of 12 glucose units. The lower molecular complexity is in agreement with the greater solubility of glycogen as compared with starch, and with the fact that only one modification of glycogen is known.

Glycogen exhibits a faint reducing action towards Fehling's solution, but it has not yet been determined whether this is a normal property or

[1] W. T. Astbury, F. O. Bell and C. S. Hanes, *Nature*, 1940, **146**, 558. [2] A sample purified and examined by Haworth, R. L. Heath and Peat, *J. C. S.*, **1942**, 55, resembled natural starch in structure, but gave a minimum unit chain length by end-group assay of 80-90 glucose units, as against 24-30 for the natural product. [3] Haworth and E. G. V. Percival, *J. C. S.*, **1932**, 2277. Haworth, Hirst and Smith, *J. C. S.*, **1939**, 1914.

whether the vigorous treatment required for the isolation of the compound from the animal tissue has affected the second terminal glucose residue in such a way as to destroy its reducing power.

Inulin (p. 315) differs from the above compounds in possessing a fundamental unit of fructofuranose, a modification of fructose containing a 1:4-oxidic ring. When methylated and submitted to hydrolysis, inulin yields a mixture of 3:4:6-trimethyl-fructofuranose together with about 3·7 per cent. of 1:3:4:6-tetramethyl-fructofuranose.[1] It is therefore concluded that the inulin molecule has the structure



Inulin.

The tetramethyl-fructofuranose is derived from the monosaccharide unit at the left-hand end of the formula, and from the proportion present in the hydrolysis mixture it is estimated that the molecule contains about 30 fructofuranose residues, and thus has a molecular weight of approximately 5000. This value is in agreement with that previously obtained for unmethylated inulin by the cryoscopic method,[2] hence there is no aggregation of the " chemical units " such as occurs with starch.

However carefully it is purified, inulin always exhibits reducing properties towards Fehling's solution ; the second terminal group appears therefore to be of the reducing type represented at the right-hand end of the formula.

Cellulose,[3] of the general formula $(C_6H_{10}O_5)_x$, is the most complex polysaccharide known, and forms the chief constituent of the cell walls of all plants. It is therefore obtainable in quantity from many natural products, among which the following rank highest in industrial importance : wood, the chief constituent of which is cellulose ; cotton-wool, distinguished by its fineness and comparative purity ; also flax, hemp, nettles and other substances. Cellulose possesses an organised tubular structure, which shows distinct minor differences according to the source of the material.

In order to obtain pure cellulose, the cellular tissue of plants, preferably cotton-wool, is treated in succession with dilute alkali, dilute acid, water, alcohol and ether. Under these conditions impurities and incrustations are removed, and the cellulose, which is very stable towards dilute acids

[1] Haworth, Hirst and E. G. V. Percival, *J. C. S.*, 1932, 2384. [2] Drew and Haworth, *J. C. S.*, 1928, 2670. [3] See *Researches on Cellulose*, 1910-1921, Cross and Dorée (Longmans) ; *The Biochemistry of Cellulose, the Polyuronides, Lignin, etc.*, by A. G. Norman (Oxford, 1937).

and alkalis, is obtained as a white amorphous mass. Textiles such as cotton and linen consist almost entirely of cellulose, and the finest Swedish filter paper is an almost chemically pure form.

Cellulose is insoluble in the usual solvents, including acids and alkalis, but dissolves in *Schweizer's reagent* made by dissolving copper hydroxide in ammonia. From this solution cellulose may be precipitated as a jelly by addition of acids, salts, etc., and on washing with alcohol is then obtained as a white amorphous powder. A similar solvent power is possessed by a solution of copper carbonate in ammonia, and by zinc chloride dissolved in hydrochloric acid.

By suitable treatment with acids, cellulose may be transformed into a hydrated cellulose or *hydrocellulose*. This is much more reactive than the original substance, and is therefore frequently used in place of the latter in technical processes requiring cellulose as raw material.

With strong sulphuric acid cellulose swells up and passes gradually into solution, from which the addition of water precipitates a substance *amyloid*, resembling starch. On prolonged treatment with strong sulphuric acid, followed by boiling with dilute acid, cellulose undergoes complete hydrolysis, yielding first dextrins, and eventually *d*-glucose. Under certain conditions the hydroxyl groups of cellulose interact with acids with the production of *esters*, among which those of nitric acid are of outstanding importance. *Acetyl derivatives* [1] of cellulose are obtained by the action of glacial acetic acid and acetic anhydride, and *cellulose aceto-sulphates* [2] by use of a mixture of glacial acetic acid, acetic anhydride and sulphuric acid. In these, as in many other cases, mixtures of products are formed showing a progressive increase in the number of substituents entering into the cellulose molecule. The change in composition is accompanied by a corresponding alteration in the physical properties of the mixture. The central position in the series is occupied by a substance known as " normal aceto-sulphate," analytical results of which are best represented by the formula $(C_{24}H_{28}O_8)(SO_4)(C_2H_3O_2)_{10}$.

If well-dried cellulose is brought into an atmosphere containing a small proportion of sulphur trioxide, the latter enters into combination in such a manner that three SO_3 molecules are taken up for each $C_6H_{10}O_5$ group. The *acid trisulphate of cellulose* so formed is stated to be a well-characterised compound which is stable in air and may be obtained analytically pure.[3]

HYDROLYSIS OF CELLULOSE

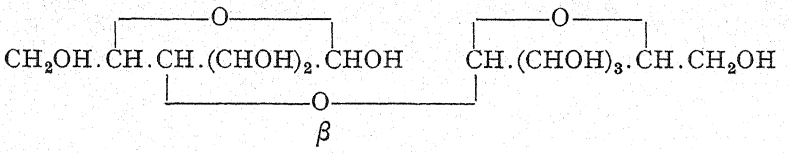
Many attempts have been made to obtain some knowledge of the constitution of cellulose by the use of hydrolytic methods. In general, the degradation of a complex polysaccharide may be said to be the result of two simultaneous processes: depolymerisation to the fundamental

[1] Cross, Bevan and Traquair, *Ch. Zeit.*, 1905, **29**, 527. [2] Cross, Bevan and Briggs, *Ber.*, 1905, **38**, 1859, 3531. [3] W. Traube, Blaser and Grunert, *Ber.*, 1928, **61**, 754.

units of the polysaccharide molecule, and disruption of these units to reducing sugars.

Among various processes for breaking down the cellulose molecule may be mentioned biochemical methods, decomposition under the influence of heat, hydrolysis with concentrated sulphuric acid or hydrochloric acid, and treatment with acetic anhydride. Under these conditions the cellulose is eventually disrupted into *cellobiose* and glucose. Dextrins are also important degradation products of cellulose. As yet they can scarcely be defined, but they obviously represent intermediate stages between the cellulose molecule and the simple sugars.

The *constitution of cellobiose* (cellose) has been examined in detail by Haworth,[1] by the method of complete methylation. From an examination of the disruption products of the octa-methyl derivative it is concluded that cellobiose is a glucose-β-glucoside of the structure [2]

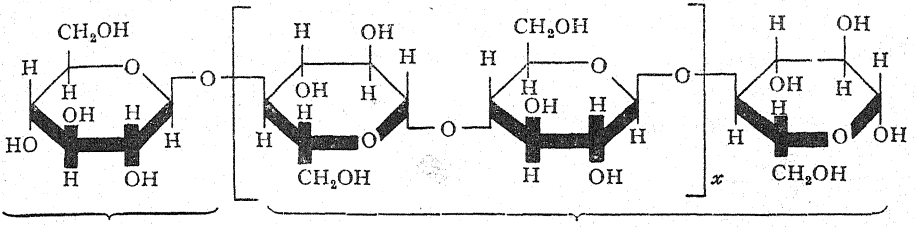


Constitution of Cellulose.—Quantitative estimates of the yield of glucose from cellulose have been made by various workers. Irvine and Soutar,[3] employing acetic anhydride and sulphuric acid as reagents, obtained a yield of crystalline glucose derivative corresponding to 85 per cent. of the theoretical; Monier-Williams,[4] using concentrated sulphuric acid alone, isolated over 90 per cent. of crystalline glucose. It thus appears that in all probability the cellulose molecule is composed solely of β-glucose residues united together by a 1:4-linking as in cellobiose.

After having established the structure of cellobiose as a glucose-β-glucoside, Haworth [5] investigated the composition of cellulose by the end-group method (see starch, p. 316). Careful hydrolysis of methylated cellulose with cold saturated hydrochloric acid gave a mixture of methylated glucoses, which was analysed by conversion into the corresponding methyl glucosides followed by fractional distillation in a high vacuum. In this manner the main product, *trimethyl glucose*, was found to be mixed with a small amount of *tetramethyl glucose*. From the presence of the latter it was inferred that, as in the case of starch, the molecules are terminated chains and not endless loops. Furthermore, the proportion of tetramethyl glucose in the mixture leads to a value of between 100 and 200 β-glucose units for the length of the chain, indicating a molecular weight of the order 20,000-40,000 for the particular cellulose preparation employed. This is regarded as a lower limiting value.

[1] Haworth, Long and Plant, *J. C. S.*, **1927**, 2809. [2] This sugar has been synthesised by K. Freudenberg and W. Nagai, *Ber.*, 1933, **66**, [B], 27. [3] Irvine and Soutar, *J. C. S.*, 1920, **117**, 1489. [4] Monier-Williams, *J. C. S.*, 1921, **119**, 803. [5] Haworth and H. Machemer, *J. C. S.*, 1932, 2270.

A model of the formula thus deduced for cellulose shows the molecules to be represented by long straight lines, in agreement with the character-



Gives rise to tetramethyl glucopyranose.

Gives rise to 2 : 3 : 6-trimethyl glucose.

istic appearance of the natural cellulose fibre (contrast starch, p. 318). This structure is also confirmed by various X-ray examinations of cellulose.[1] It has been estimated [2] from the breadth of the lines measured along the fibre axis in the X-ray diagram of native ramie cellulose that the minimum molecular weight is 20,000. This value is of the same order as that determined chemically by end-group analysis.

Later researches,[3] however, indicate that some modification of the above conclusions is required. It has been found that the amount of end-group fraction isolated increases with the number of methylations to which the material has been submitted, indicating a progressive disaggregation of the molecules. Moreover, after five methylations conducted in an atmosphere of nitrogen, no tetramethyl glucose end-group could be detected and the molecular weight deduced by physical methods corresponded to about 1000 glucose units as compared with 100-120 units after six methylations in air. Even in nitrogen disaggregation takes place, leading after 25-30 methylations to a minimal value of about 200 glucose units. According to experimental conditions, therefore, methylated celluloses may be formed which are either terminated chains of glucose or closed chains with no terminal glucose unit.

Pending further information it is suggested that the cellulose structure is represented by long parallel chains of the type illustrated above, so orientated that alternate chains are arranged with their potential reducing groups pointing in opposite directions ; the ends of the chains are supposed to be united in pairs to form long closed loops, whose semi-rigid parallel alignment is maintained by a series of bonds linking opposite sides of the loops. On methylation in nitrogen the loop may be ruptured, but this must be followed by the open ends uniting to give smaller closed loops. In air the ruptured ends apparently remain open.[4]

[1] For the X-ray investigation of cellulose see *Colloid Symposium Monograph*, New York, 1926, 174 ; Sponsler, *J. Gen. Physiol.*, 1926, **9**, 677 ; K. H. Meyer and Mark, *Ber.*, 1928, **61**, 593 ; K. H. Meyer, *Zeit. angew. Chem.*, 1928, **41**, 935 ; Staudinger, *ibid.*, 1929, **42**, 37, 67. [2] R. O. Herzog and Krüger, *J. Physical Chem.*, 1926, **30**, 466. Hengstenberg, *Z. Krist.*, 1928, **69**, 271. [3] W. N. Haworth, E. L. Hirst, L. N. Owen, S. Peat and F. J. Averill, *J. C. S.*, 1939, 1885. W. N. Haworth, R. E. Montonna and S. Peat, *ibid.*, p. 1899. [4] For a more detailed account see Haworth, *Chem. and Ind.*, 1939, **58**, 917 ; S. Peat, *Ann. Rep.*, 1939, 273.

Other Properties of Cellulose.—Towards dilute alkalis, which readily dissolve and decompose animal tissue, cellulose is extremely stable. A strong solution of caustic alkali, on the other hand, produces a curious thickening and gelatinisation of the walls of the fibre, causing the cellulose to shrink and become translucent. This reaction is used for producing crinkled surfaces on cotton fabrics, the process being known as *mercerising*, after its discoverer.[1] Alkali celluloses, produced in the above manner by the action of concentrated alkalis, combine with carbon bisulphide to form a mixture of *cellulose xanthates* known as **viscose.**[2] These are sodium salts of the general formula RO.CS.SNa, which swell up with water to a marked degree, giving a colloidal solution which has become of great importance in the manufacture of artificial silk. The solution is stable in the cold and in the absence of oxygen, but in air it is gradually decomposed with regeneration of cellulose. It is also employed for the impregnation of paper and fabrics, and in calico printing. The action of oxidising agents on cellulose leads to the formation of *oxycelluloses*.

As already indicated, cellulose is used industrially in a variety of ways, *e.g.* in the preparation of oxalic acid (p. 270), paper, parchment paper, collodion, gun-cotton, smokeless powder, celluloid and artificial silk.

The following is a short description of the chemical processes involved in the **manufacture of paper.** A preliminary treatment is given with the object of effecting a clean separation of the wood cellulose from the encrusting lignin, xylan and other complex substances which cement the cells together into a rigid mass. Two processes are in use for the manufacture of paper from wood, straw, esparto grass, etc.: (*a*) The *caustic soda process*, in which the finely divided wood is boiled (160° to 170°) in iron vessels with dilute caustic soda for several hours under a pressure of 6 to 8 atmospheres. Under this treatment certain compounds known collectively under the name of lignin[3] are removed. The cellulose is then washed with water and is ready for working up. Cellulose which has been purified with caustic soda forms soft threads of small resisting capacity. A harder and more valuable product is given by (*b*) the *sulphite process*, in which the wood is heated under increased pressure with a solution of calcium or magnesium bisulphite. These reagents also dissolve the enveloping lignin, but have little action on the cellulose fibre.

In the **preparation of parchment paper,** unsized paper (filter paper) is immersed for a few seconds in concentrated sulphuric acid which has been diluted with half its volume of water. It is then washed with water and finally with ammonia. A layer of amyloid is formed on the surface of the paper, rendering it like parchment in appearance, and comparatively impermeable to water.

Cellulose Nitrates, or Nitrocelluloses

A mixture of nitric and sulphuric acids interacts with cotton-wool to form nitric esters of cellulose, incorrectly but very generally known

[1] In 1844 John Mercer observed that cellulose which had been treated at the ordinary temperature with caustic soda showed, after washing and drying, an increased tenacity and power of taking up certain dyes. Later it was found that cotton so treated acquired a higher lustre, and hence mercerisation became an industrial process. [2] Cross, Bevan and Beadle, *Ber.*, 1893, **26**, 1090; 1901, **34**, 1513. [3] The presence of lignin in cellulose or paper is easily recognised by the development of a red colour on testing with a solution of phloroglucinol in hydrochloric acid.

as nitrocelluloses. These still retain the structure of cotton-wool, although somewhat coarser and harder to the touch. By modifying the concentration of acid used and the length of treatment it is possible within limits to vary the number of nitric acid groups entering into the cellulose molecule. The ester with the lowest proportion of nitrogen has the composition of a dinitrate of cellulose, $C_{12}H_{18}O_8(ONO_2)_2$, while that containing the highest proportion approximates closely to a hexanitrate,[1] $C_{12}H_{14}O_4(ONO_2)_6$. The product obtained, however, is always a mixture, and a gradual alteration in the conditions of nitration never leads to any sudden change in the proportion of nitrogen. No sharp distinction can therefore be drawn between di-, tri- and tetranitrocelluloses, and so on. An important factor is the water content of the nitrating acids; if this is increased the nitrogen content of the product decreases regularly, although not proportionally, within the above limits. Probably the nitration of cellulose leads to the formation of a mixture of compounds in which a progressively increasing number of complexes have entered into reaction. In addition to esterifying the cellulose, nitric acid also brings about hydration, leading to the formation of hydrocellulose nitrates.

Lower nitrocelluloses containing from two to four nitro groups burn very much more freely than cellulose itself, but are in no sense explosive. They are grouped together under the name of **pyroxylin,** and dissolve readily in a mixture of alcohol and ether, such a solution being sold as **collodion.** The latter is extensively used in medicine, photography and the manufacture of artificial silk (see below).

If lower nitrates of cellulose are mixed with camphor and submitted to the action of heat, **celluloid** is obtained. The warm product is easily moulded, and sets to a hard, transparent mass on cooling. It is employed in the manufacture of a variety of useful and ornamental articles, but is very inflammable.[2]

For the preparation of celluloid, 10 parts of nitrated and specially treated tissue paper are intimately mixed with an alcoholic solution of 4 to 5 parts camphor, to which may be added colouring matter. The mixture is kneaded at about 90° in closed iron vessels, rolled out into plates, and dried at a moderate temperature.

Celluloid may be considered as an intimate physical mixture of nitrocelluloses and camphor. Nevertheless, its behaviour in some ways resembles that of a true chemical compound, since it no longer possesses the properties of a simple mixture of its components, and cannot be separated into the latter by mechanical means without great difficulty.

Owing to the comparatively high price of camphor many attempts have been made to replace it wholly or in part by other substances, but so far no satisfactory substitute has been discovered.

[1] The actual formulæ of the nitrates are, of course, higher multiples of the above.
[2] A product similar to celluloid is used under the name of *galalith*. It is prepared from casein by interaction with formaldehyde, has no odour, and is not dangerously inflammable. *Cellon*, prepared from cellulose acetate (cellite) by the addition of camphor, is also less inflammable than celluloid.

The highest nitration product of cellulose has a nitrogen content approaching that of a cellulose hexanitrate (p. 325), and is employed under the name of **gun-cotton** in propellant explosives and for blasting. Gun-cotton burns with extreme rapidity but only explodes when detonated, *e.g.* when combustion is initiated by means of a little mercury fulminate. For explosive purposes it may be used directly in the compressed state, as in torpedoes and in cartridges for blasting, or it may be employed mixed with nitroglycerine (p. 251). A development of great importance was the utilisation of gun-cotton and pyroxylin in the preparation of **smokeless powder**. This is based on the fact that when nitrocelluloses are treated with solvents such as acetone or ethyl acetate, even in quantity insufficient for solution, they completely lose their organised structure. Under this treatment they swell up, forming a gelatinous product, which, after removal of the solvent, gives an amorphous mass of the same chemical composition as the starting material, but possessing a much closer texture. In such a product the explosion wave is propagated with much lower velocity, thus rendering it suitable for use as a propellant. Nitrocellulose powders of this type have been adopted by the ordnance departments of almost every army. The explosive is employed in the form of small squares for rifles, and in ribbons or bundles of rods for artillery. In the British and Italian armies, and in certain navies, powders are also in use which contain a considerable proportion of nitroglycerine in conjunction with nitrocellulose. This mixture is known as cordite.

Nitrocellulose is further of great industrial value in the preparation of artificial silk.

Artificial Silk

The preparation of artificial silk consists essentially in forcing a syrupy solution of cellulose, cellulose derivatives, or other products under high pressure through very fine apertures into a suitable medium, whereby the solvent is removed and fine threads are obtained. The threads are allowed to form under slight tension, and as soon as they have solidified are twisted or collected directly on reels, to be woven subsequently into fabrics in the same way as natural silk.

The practical difficulties of this process were first overcome in 1885 by de Chardonnet, who employed collodion as the starting material. This gave a thread consisting of nitrocellulose and therefore exceedingly inflammable. By treatment with denitrating agents, *e.g.* sodium hydrosulphide, it was found possible to replace the nitrate grouping in the nitrocellulose threads by hydroxyl without altering the form of the material. Threads consisting of cellulose or a hydrate of cellulose are thus formed, which are no more inflammable than ordinary cotton. At the present time large quantities of artificial silk manufactured in this way are used under the name of *Chardonnet* or **collodion silk.**

Cellulose threads possessing the desired silky gloss are also obtained by other methods, *e.g.* by utilising a solution of cellulose in ammoniacal copper oxide as the "spinning liquid" (Pauly's method). In this case the liquid is forced into dilute sulphuric acid, which coagulates the threads and at the same time removes copper and ammonia, yielding without any further treatment a cellulose thread.

A product known as **viscose silk** is manufactured by use of a solution of cellulose xanthates (p. 324). The threads at first consist of viscose, but when dried and submitted to treatment, which need not be described in detail, carbon bisulphide and alkali are eliminated and cellulose is formed.

Artificial silks in which the thread is composed of cellulose are collectively known as *rayons*. All these varieties possess a high lustre and pure white colour, and may be obtained without difficulty in all shades by dyeing in the usual manner as for cotton. They have, however, a low tensile strength, especially in the moist state.

A material of different type is **acetate silk** containing a thread of acetylated cellulose. The spinning liquid is here a mixture of acetates formed by treating cellulose with acetic anhydride and acetic acid, with addition of either sulphuric acid or zinc chloride. It possesses a good lustre and great tenacity, and is insensitive to moisture. Acetate silk is, however, less readily dyed than rayon.

Nylon, a similar product formed from synthetic complex amides, is used as a substitute for hog's bristles and for many other purposes. It can be obtained in exceedingly fine threads (see p. 859).

XVIII

Cyanogen Compounds

Cyanogen, *dicyanogen, oxalo-nitrile,* C_2N_2, was discovered in 1815 by Gay-Lussac. It is the first known example of a "compound radical" occurring unchanged throughout a whole series of derivatives, and playing in every case the part of a monovalent element. It behaves in many respects like the halogens, forming, for example, a hydrogen compound HCN, hydrocyanic acid, which strongly resembles the hydrogen halides in its properties.

Cyanogen, N ⋮ C.C ⋮ N, is the nitrile of oxalic acid and can be prepared from ammonium oxalate by heating it with dehydrating agents.

$$C_2O_4(NH_4)_2 - 4H_2O = C_2N_2$$

It is also formed by heating mercuric cyanide, $Hg(CN)_2 = Hg + C_2N_2$. In this reaction a brown amorphous polymer of cyanogen called *paracyanogen* remains behind, the molecular weight of which is unknown. Cyanides of gold and silver decompose in a similar manner under the influence of heat. Cyanogen is usually prepared by heating a solution of copper sulphate with potassium cyanide.

$$2CuSO_4 + 4KCN = Cu_2(CN)_2 + C_2N_2 + 2K_2SO_4$$

It is a colourless, very poisonous gas of pungent smell; it condenses to a liquid at −25°, and burns with a bluish-red flame. In aqueous solution it decomposes rapidly, forming a brown, amorphous mass known as *azulmic acid*.[1]

Hydrogen cyanide, prussic acid, HCN, is found in the free state in certain tropical plants, and is formed from the glucoside *amygdalin*, by the hydrolytic action of the enzyme emulsin, both of these compounds being present in bitter almonds:

$$\underset{\text{Amygdalin}}{C_{20}H_{27}O_{11}N} + 2H_2O = \underset{\text{Benzaldehyde}}{C_7H_6O} + HCN + 2\underset{d\text{-Glucose.}}{C_6H_{12}O_6}$$

A very dilute solution of hydrogen cyanide obtained in this manner is used medicinally.

Hydrocyanic acid is best prepared by the action of concentrated sulphuric acid (diluted with an equal volume of water) upon a warm strong solution of sodium cyanide. Hydrogen cyanide escapes as a gas and can be condensed by use of a freezing mixture.

Hydrocyanic acid may also be prepared by heating potassium ferrocyanide with dilute sulphuric acid.

$$2K_4Fe(CN)_6 + 3H_2SO_4 = K_2Fe_2(CN)_6 + 3K_2SO_4 + 6HCN$$

[1] For the reactions of cyanogen see Vorländer, *Ber.*, 1911, 44, 2455.

Hydrogen cyanide is also formed from acetylene and nitrogen under the influence of the electric arc, and is present in crude coal gas. It was originally prepared from Prussian blue, thus giving rise to the terms prussic acid and cyano-compound (from the Greek root signifying "blue").

In the anhydrous state hydrocyanic acid is a colourless liquid with a peculiar smell, reminiscent of bitter almonds. It boils at 26°, and solidifies to a crystalline mass at −14°. It is one of the weakest acids, and like most cyano-derivatives is exceedingly poisonous. Hydrocyanic acid readily combines with water, even on standing in solution, to form ammonium formate, from which it is easily regenerated by distillation. On reduction it yields methylamine, $HCN+4H=CH_3.NH_2$. It unites directly with the carbonyl groups of aldehydes and ketones (see p. 179), and adds on to the double bond of ethylene derivatives. Phenyl isocyanate reacts with it to form cyano-formanilide.

$$HCN+C_6H_5.N:C:O = C_6H_5.NH.CO.CN$$

The addition of HCN to organic compounds is found to be initiated, or greatly accelerated, by the presence of alkalis or organic bases, and on the other hand is prevented or retarded by mineral acids. According to Lapworth,[1] this is connected with ionisation and the intermediate formation of complex ions.

The *constitution of hydrocyanic acid* as the nitrile of formic acid, H.C⋮N, is deduced from its production from ammonium formate and the ease with which it may be converted into the latter. It gives rise, however, to two distinct series of alkyl derivatives, namely, the cyanides R.C⋮N and the isocyanides R.N:C or R.N⋮C (see p. 214), and recently the formula H.N⋮C has also been considered for the free acid. In any case, the acid must be classed as a liquid tautomeric compound, and hence should be regarded as an equilibrium mixture of the two possible forms HCN and HNC. Under ordinary conditions the compound appears to consist almost entirely of the form H.C⋮N.

Simple and Complex Salts of Hydrocyanic Acid.—Alkali cyanides are formed on heating nitrogenous organic matter with the requisite metals. Like the cyanides of the alkaline earths and of mercury, they are readily soluble in water, whereas the cyanides of the remaining metals are for the most part insoluble.

Potassium cyanide can be prepared by heating potassium ferrocyanide in the absence of air.

$$K_4Fe(CN)_6 = Fe+C_2+N_2+4KCN$$

It is used as a solvent for silver salts in photography, for the preparation of various double cyanides in electro-deposition, and for the extraction of gold. When metallic gold dissolves in a solution of potassium cyanide, a double salt of the formula $KAu(CN)_2$ is formed, with absorption of atmospheric oxygen according to the equation

$$2Au+4KCN+2H_2O+O_2 = 2KAu(CN)_2+2KOH+H_2O_2.$$

[1] Lapworth, *Proc. Chem. Soc.*, 1903, **19**, 189; **20**, 54.

The hydrogen peroxide set free enables an additional amount of gold to pass into solution.

$$2Au+4KCN+H_2O_2 = 2KAu(CN)_2+2KOH$$

Metallic gold may be obtained from the compound $KAu(CN)_2$ by electrolysis or precipitation with metallic zinc.

Owing to the demand for potassium cyanide for these purposes, it has recently been prepared synthetically by leading ammonia or nitrogen over a red-hot mixture of charcoal and potassium carbonate. Efforts have also been made to prepare it commercially from calcium cyanamide. In the former process potassium cyanate is first produced, which is then converted into potassium cyanide, probably as a result of the reducing action of the charcoal.

$$K_2CO_3+NH_3 = KOCN+H_2O+KOH$$
$$KOCN+C = KCN+CO$$

Potassium cyanide is obtained from the crude product by extraction with water, and salting it out of the concentrated solution by addition of potassium carbonate.

It is almost insoluble in absolute alcohol, but dissolves readily in water. In aqueous solution it rapidly decomposes to give potassium formate and ammonia, $KCN+2H_2O=HCOOK+NH_3$. Its power of undergoing double decomposition with halogen substitution products of organic compounds is frequently used for the introduction of the cyano group. *Silver cyanide*, AgCN, is obtained by precipitating potassium cyanide with silver nitrate. With excess of the first reagent it forms a beautifully crystalline double compound, $KAg(CN)_2$, which is used for electroplating, just as the double cyanides of gold and nickel are employed for the electro-deposition of these metals.

This tendency to form complex salts is characteristic of the cyanides, and in certain cases the metal and cyanogen are united in such a manner that neither of them responds to the usual tests. Among such compounds are *potassium ferrocyanide* or *yellow prussiate of potash*, $K_4Fe(CN)_6+3H_2O$, and *potassium ferricyanide* or *red prussiate of potash*, $K_3Fe(CN)_6$. These are salts of hydroferrocyanic acid, $H_4Fe(CN)_6$, and hydroferricyanic acid, $H_3Fe(CN)_6$, respectively,[1] and are described in detail in text-books of inorganic chemistry. Potassium ferro- and ferricyanides are complex salts containing the electro-negative radical, $Fe(CN)_6$. On ionisation in solution they break up into the complex anions $Fe(CN)_6$ and potassium cations. The ferricyanide is less stable than the ferrocyanide, and for this reason is poisonous, as it decomposes to give hydrogen cyanide when taken internally. It may also be mentioned that potassium ferrocyanide, which is the starting material in the preparation of the above cyanogen compounds, has been obtained from early times by heating nitrogenous animal refuse (such as blood, horn, hoofs, and hair) with potassium carbonate and iron (or iron ore). Recently this method has been

[1] Hydroferricyanic and hydroferrocyanic acids possess in a high degree the property of yielding well-defined oxonium salts (p. 160).

abandoned and the salt is now prepared by absorbing hydrogen cyanide in a suspension of ferrous hydroxide or ferrous carbonate in aqueous potassium carbonate, or by treating Prussian blue with potassium hydroxide. Hydrogen cyanide and other cyanogen derivatives are obtained as by-products in the manufacture of coal gas and coke.

Potassium ferricyanide is prepared from potassium ferrocyanide by oxidation with chlorine,

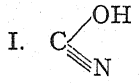
$$2K_4Fe(CN)_6 + Cl_2 = 2K_3Fe(CN)_6 + 2KCl$$

With reference to the constitution of hydroferro- and hydroferricyanic acids, it is assumed by many that both contain the trivalent radical C_3N_3 of cyanuric acid.

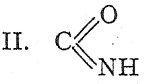
Alkyl derivatives of hydrogen cyanide, i.e. nitriles and isonitriles, have already been discussed in Chapter XI.

Cyanic Acid, Cyamelide, and Cyanuric Acid

Cyanic acid, HCNO, may be represented by either of the two possible structures I and II.



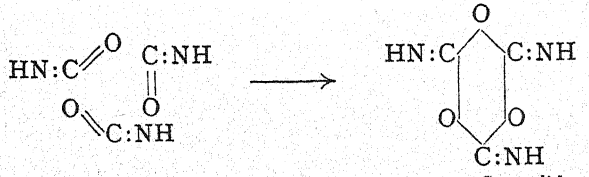
Cyanic acid



Isocyanic acid.

Only one cyanic acid, however, is known. This is obtained by the action of heat on cyanuric acid, and forms a colourless liquid which is unstable above 0°. As will be seen later, the acid is tautomeric, yielding derivatives corresponding to both of the types I and II. In accordance with the modern views on tautomeric fluid compounds, it may be regarded as an allelotropic mixture (p. 64) of these two forms.

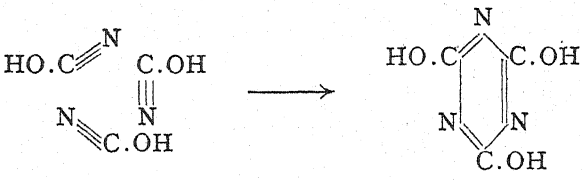
At temperatures above 0° liquid cyanic acid is transformed with explosive violence into **cyamelide,** of the formula $(CNOH)_3$. This is probably formed by the polymerisation of isocyanic acid, combination taking place between carbon and oxygen in the manner shown below. Cyamelide is a white, porcelain-like mass which is insoluble in water. On being heated it is depolymerised to cyanic acid. When heated with water the cyanic acid first produced decomposes slowly into ammonia and carbon dioxide.



Isocyanic acid. Cyamelide.

Cyanuric acid, $(CNOH)_3$, another polymeride of cyanic acid, was discovered long ago by Scheele during the dry distillation of urea, $CO(NH_2)_2$. Under the influence of heat the urea first breaks up into

ammonia and cyanic acid, and the latter, by union between carbon and nitrogen, immediately polymerises to cyanuric acid :

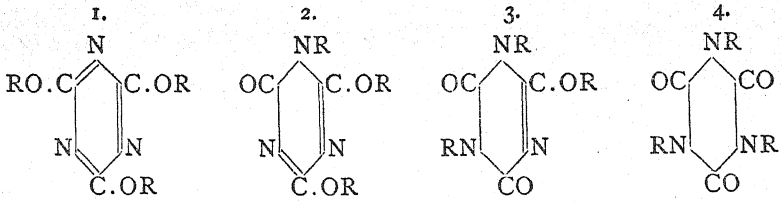


Cyanic acid Cyanuric acid.

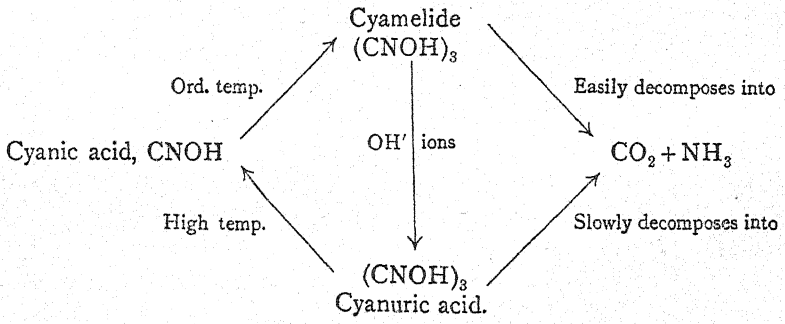
Cyanuric acid is also formed from cyanuric bromide (obtained by the action of bromine on potassium ferricyanide) by warming with water ; and by the isomerisation of cyamelide, which is effected slowly and partially on boiling with water, or more rapidly and completely with alkalis.

It is a tribasic acid which crystallises in rhombic prisms. On prolonged boiling with hydrochloric acid it decomposes into carbon dioxide and ammonia.

Cyanuric acid contains the radical $(CN)_3$, in which carbon and nitrogen are linked alternately to form a closed ring. The solid acid is a tricarbimide of type 4 (below), and therefore a pseudo-acid. Hence it is known as pseudo-cyanuric or isocyanuric acid.[1] The three pseudo-groups, CO.NH, are capable of isomerising into the salt-forming groups, C(OH) : N, giving rise to four types of derivatives, as illustrated by the following formulæ of the isomeric *trialkyl esters of cyanuric acid* [2] :



Cyanuric acid and cyamelide are therefore polymerides of cyanic acid possessing different constitutions. The relationship between these three compounds is illustrated in the following diagram [2] (Hantzsch) :



[1] Hantzsch, *Ber.*, 1906, **39**, 139. [2] Hantzsch and Bauer, *Ber.*, 1905, **38**, 1005.

Derivatives of Cyanic and Isocyanic Acids

A derivative of normal cyanic acid, HO.C≡N, is **cyanogen chloride,** Cl.C≡N, prepared by the action of chlorine on metallic cyanides or hydrocyanic acid, $HCN+Cl_2 = NC.Cl+HCl$. It is a very poisonous liquid which boils at 14·5°, readily polymerises to cyanuric chloride, $C_3N_3Cl_3$, and on treatment with potassium hydroxide yields potassium chloride and potassium cyanate.

$$NC.Cl+2KOH = NCOK+KCl+H_2O$$

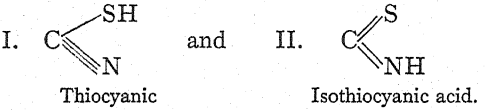
Esters of normal cyanic acid have not yet been isolated, but **isocyanic esters,** O:C:NR, derived from the pseudo-acid are well known. The latter are obtained by heating salts of alkyl-sulphuric acids with potassium cyanate, or alkyl iodides with silver cyanate (cyanuric esters being also formed).

$$OCNAg+I.C_2H_5 = O:C:N.C_2H_5+AgI$$

They are liquids of exceedingly pungent smell which boil without decomposition. When heated with alkali they decompose into carbon dioxide and primary amines. With ammonia and amines they unite to form derivatives of urea, $C_2H_5.NCO+NH_3 = C_2H_5.NH.CO.NH_2$, and with alcohol to form derivatives of carbamic acid. Esters of isocyanic acid gradually polymerise to cyanuric esters.

Thiocyanic Acid and Derivatives

Thiocyanic acid, *sulphocyanic acid,* HCNS, corresponds to cyanic acid, and like the latter may react in two forms :



Thiocyanic acid. Isothiocyanic acid.

Only one thiocyanic acid is known, which may be obtained by treating barium thiocyanate with an equivalent proportion of sulphuric acid, or dry mercury thiocyanate with gaseous hydrogen sulphide. It is a very volatile liquid with an acrid smell, and like cyanic acid readily passes into a solid polymeride. The free acid and its soluble salts give an intense red coloration with faintly acid solutions of ferric salts, a reaction used as a sensitive test for the ferric ion. The colour depends on the presence of the unionised compound, $Fe_2(CNS)_6$.

Potassium thiocyanate, CNSK, is obtained by fusing together potassium cyanide and sulphur. It dissolves readily in water with considerable absorption of heat. *Sodium thiocyanate* occurs in the saliva and urine of various animals. *Ammonium thiocyanate,* $CNS(NH_4)$, is prepared from carbon bisulphide and ammonia.

$$CS_2+2NH_3 = CNS(NH_4)+H_2S$$

It forms deliquescent crystals, which on heating at 160° are transformed into thiourea, and at 180° into guanidine thiocyanate. *Silver thiocyanate,* CNSAg, is deposited as a precipitate resembling silver chloride during the volumetric estimation of silver by Volhard's method. *Mercury thiocyanate* may be obtained as a grey amorphous precipitate; when moulded into pellets, dried and ignited, it forms long snake-like tubes of ash (Pharaoh's serpents).

Esters of normal thiocyanic acid, of the formula $N\equiv C—S.R$, are obtained by heating potassium thiocyanate with potassium alkyl sulphates or alkyl iodides.

$$CN.SK+C_2H_5I = NC.SC_2H_5+KI$$

They are liquids smelling of garlic, and are insoluble in water. On reduction with zinc and sulphuric acid they yield hydrocyanic acid and mercaptans,

$$NC.S.C_2H_5+2H = HCN+HS.C_2H_5$$

and when heated they partially isomerise into isothiocyanic esters.

The *esters of iso-* or *pseudo-cyanic acid*, $S:C:N.R$, are known as **mustard oils,** and occur in various plants as glucosides of imino-thiocarbonic acid, of the type

$$\text{Glucose—}S—\underset{\displaystyle OR'}{\overset{\displaystyle |}{C}}=N.R$$

In addition to being formed by isomerisation of the normal esters, they are obtained by the action of mercuric or ferric chloride on amine salts of alkyl dithio-carbamic acids (prepared by the combination of carbon disulphide and amines).

$$2C_2H_5NH_2+CS_2 \longrightarrow CS\begin{matrix}\diagup SH,\ NH_2C_2H_5\\ \diagdown NHC_2H_5\end{matrix}$$
$$\longrightarrow S:C:NC_2H_5+H_2S+NH_2C_2H_5$$

They are lachrymatory liquids of extremely pungent odour, which are almost insoluble in water.

When heated to 100° with hydrochloric acid or to 200° with water they are hydrolysed to primary amines, carbon dioxide and hydrogen sulphide.

$$S:C:N.C_2H_5+2H_2O = H_2N.C_2H_5+CO_2+H_2S$$

Under the influence of strong sulphuric acid they yield primary amines and carbon oxysulphide.

$$S:C:NC_2H_5+H_2O = H_2NC_2H_5+S:C:O$$

On reduction they are converted into a primary amine and thioformaldehyde.

$$S:C:NC_2H_5+4H = H_2NC_2H_5+SCH_2$$

These reactions prove that in mustard oils the alkyl groups are linked to nitrogen.

The best known representative of this class is **allyl mustard oil** (*ordinary mustard oil*), $S:C:N.CH_2.CH:CH_2$, which may be obtained from the seeds of black mustard (*Sinapis nigra*) by distillation with water. It is a colourless liquid, b.p. 148°, the vapour of which is exceedingly pungent and lachrymatory. The liquid raises blisters on the skin.

Sinigrin, *potassium myronate*, is the parent substance of the natural allyl mustard oil. It is a glucoside of the formula $CH_2:CH.CH_2.N:C<\begin{matrix}SC_6H_{11}O_5\\ OSO_2OK.\end{matrix}$

This structure was first advanced by Gadamer and later confirmed by Schneider and Wrede,[1] who isolated thio-glucose from the compound. Sinigrin forms white crystals which dissolve readily in water and sparingly in alcohol.

Cheirolin, (γ-thiocarbimido-propylmethylsulphone), $CH_3.SO_2.(CH_2)_3.NCS$, the mustard oil of wallflower seed, has been prepared synthetically. It distils at 165° to 168° (6 mm.) as a colourless oil which solidifies to a white crystalline mass, m.p. 44°.

Erysolin, $CH_3.SO_2.(CH_2)_4.N:C:S$, a homologue of cheirolin, has been isolated from the seeds of *Erysimum perowskianum* and also synthesised.[2]

Cyanamide and Derivatives

Cyanamide may react in accordance with either of the formulæ $N{:}C.NH_2$ and $HN:C:NH$, and it is not known with certainty which of these structures represents the solid compound. It is formed from ammonia and cyanogen chloride, and also by treating thiourea with mercuric oxide or lead hydroxide.

$$\underset{\text{Thiourea}}{NH_2—CS—NH_2} = \underset{\text{Cynamide.}}{NCNH_2}+H_2S$$

Cyanamide is a colourless crystalline compound, which melts at 40° and readily polymerises. At 150° it is transformed into trimolecular *cyanuramide* or *melamine*, $C_3N_3(NH_2)_3$.

On the one hand it behaves as a weak base, and with strong acids forms salts which are hydrolysed by water. On the other hand it shows the properties of a weak acid, yielding metallic salts such as the technically important calcium cyanamide, and a yellow silver salt which is insoluble in ammonia.

Calcium cyanamide, $CaCN_2$, is prepared by heating a mixture of lime and coke in an atmosphere of nitrogen in an electric furnace.

$$CaO+2C+2N = CaCN_2+CO$$

The product so obtained is extensively used as an artificial manure, as it decomposes slowly with water to give ammonia.

$$CaCN_2+3H_2O = CaCO_3+2NH_3$$

In this manner it is possible to prepare ammonia indirectly from atmospheric nitrogen, and the process is of great value from the agricultural point of view.

It is also possible to use calcium cyanamide in the preparation of alkali cyanides, which are required in quantity for the extraction of gold. For this purpose the compound is first boiled with water, when dicyandiamide is formed.

$$2CaCN_2+4H_2O = 2Ca(OH)_2+(CN.NH_2)_2$$

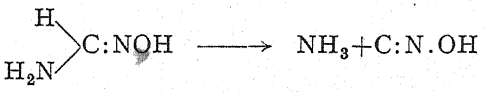
The latter, on fusion with a mixture of carbon and soda or potash, is then converted into alkali cyanide and ammonia, melamine also being produced.

$$(CN.NH_2)_2+Na_2CO_3+2C = 2NaCN+NH_3+H+3CO+N$$

[1] W. Schneider and Wrede, *Ber.*, 1914, **47**, 2225. [2] W. Schneider, *Ann.*, 1910, **375**, 207; *Ber.*, 1913, **46**, 2634.

Fulminic Acid

Fulminic acid, *carbonyl oxime*, C:N.OH, is regarded as the oxime of carbon monoxide,[1] and possesses the properties of a strong acid. It is a very unstable, volatile compound, with a smell recalling that of hydrocyanic acid. Like the latter it is very poisonous. It is formed when fulminates are treated with strong acids and also by the decomposition of formamidoxime (isuretin).



Mercury fulminate, $(CNO)_2Hg$, is the most important of the salts. It was discovered by Howard in 1799, and is largely used in percussion caps as a detonator for explosives. It is prepared technically by dissolving mercury in an excess of strong nitric acid, with the subsequent addition of alcohol. **Silver fulminate** may be obtained in a similar manner; it is much more explosive than the mercury compound, and is used in the manufacture of crackers.

XIX

Derivatives of Carbonic Acid

Carbon dioxide is the anhydride of the very unstable carbonic acid, H_2CO_3 or $O:C(OH)_2$, which may also be considered as hydroxy-formic acid, HO.COOH. Owing to the influence of the carbonyl group on the adjacent hydroxyl groups, the acid is dibasic. Carbonic acid and its salts are described in inorganic text-books, and only a few of its derivatives will be treated here.

I.—ESTERS AND ACID CHLORIDE OF CARBONIC ACID

Esters of carbonic acid, $CO(OR)_2$, are prepared by the action of alkyl iodides on silver carbonate, or of alcohols on carbonyl chloride, $COCl_2$. They are ethereal smelling liquids and are soluble in water, in which they gradually decompose. *Esters of ortho-carbonic acid*, $C(OR)_4$, are derived from the hypothetical ortho-carbonic acid, $C(OH)_4$, and are formed by the action of sodium alcoholates on chloropicrin, $CCl_3.NO_2$. These are also ethereal smelling liquids.

$$CCl_3.NO_2+4NaOCH_3 = C(OCH_3)_4+3NaCl+NaNO_2$$

Carbonyl chloride, *phosgene*, $COCl_2$, is produced by direct combination of carbon monoxide and chlorine at 100° in the presence of activated charcoal, or by exposing a mixture of gaseous chlorine and carbon monoxide to the direct rays of the sun. In the laboratory it is more conveniently obtained by the action of sulphur trioxide on carbon tetrachloride.

$$CCl_4+2SO_3 = COCl_2+S_2O_5Cl_2$$ Pyrosulphuryl chloride.

[1] H. Wieland, *Ann.*, 1906, **347**, 233; **350**, 390. *Ber.*, 1907, **40**, 418; 1909, **42**, 820, 1346.

By the use of 45 per cent. oleum (pyrosulphuric acid), carbonyl chloride and chlorosulphonic acid are formed almost quantitatively at 78°, according to the equation

$$SO_3+H_2SO_4+CCl_4 = COCl_2+2SO_3HCl$$

In the presence of catalysts, however, of which infusorial earth is the most satisfactory, the reaction can be brought about by the use of sulphuric acid alone.[1]

$$2H_2SO_4+3CCl_4 = 3COCl_2+4HCl+S_2O_5Cl_2$$

Although a colourless gas at ordinary temperatures, carbonyl chloride readily condenses to a liquid of boiling-point 8°, in which form it is brought on to the market. It has a very penetrating, choking smell, readily dissolves in glacial acetic acid, benzene and other hydrocarbons, and owing to the mobility of the chlorine atoms is very reactive. When heated with water it decomposes into carbon dioxide and hydrochloric acid, $COCl_2+H_2O = CO_2+2HCl$. With alcohol the first product is *chloro-carbonic ester*,

$$COCl_2+HOC_2H_5 = Cl.CO.OC_2H_5+HCl$$

and finally *carbonic ester*,

$$COCl_2+2HOC_2H_5 = CO(OC_2H_5)_2+2HCl$$

With ammonia it yields *urea*, the *diamide of carbonic acid*,

$$COCl_2+2NH_3 = CO(NH_2)_2+2HCl$$

Phosgene is employed industrially in the preparation of di- and tri-phenyl methane dye-stuffs.

Chloro-carbonic esters, also known as *chloro-formic esters*, of the general formula Cl.CO.OR, are produced as mentioned above by the action of alcohols on phosgene. They are best obtained by adding the desired alcohol to strongly cooled liquid phosgene. They are volatile liquids of pungent smell, which are used for introducing the group —CO.OR into organic compounds. With organo-magnesium halides they interact to give esters of carboxylic acids.

$$R'MgBr+Cl.COOR = R'.COOR+MgClBr$$

II.—AMIDES OF CARBONIC ACID

The dibasic nature of carbonic acid is also shown in the formation of two amides, viz., carbamic acid, a mono-amide, $HO.CO.NH_2$, and urea, a diamide, $CO(NH_2)_2$. With these compounds should be grouped guanidine, $C:NH(NH_2)_2$.

Carbamic acid, $HO.CO.NH_2$, is not known in the free state, but only in the form of salts and esters. *Ammonium carbamate* is produced as a white mass by the combination of dry carbon dioxide and dry ammonia, $CO_2+2NH_3 = CO(ONH_4)(NH_2)$, and is present in commercial ammonium carbonate. On being warmed to 60° in aqueous

[1] Grignard and Urbain, *C.*, 1919, **III**, 989.

solution it takes up a molecule of water and is converted into ammonium carbonate, $CO(ONH_4)(NH_2)+H_2O = CO(ONH_4)_2$.

Esters of carbamic acid are known as **urethanes.** They may be prepared by the action of ammonia on carbonic or chloro-carbonic esters at the ordinary temperature :

$$Cl.CO.OC_2H_5+NH_3 = NH_2.CO.OC_2H_5+HCl$$
$$C_2H_5O.CO.OC_2H_5+NH_3 = NH_2.CO.OC_2H_5+C_2H_5OH$$

Ethyl carbamate (urethane).

also by heating acid azides with alcohols.

The urethanes crystallise well, distil without decomposition, and are soluble in alcohol, ether and water. With alkalis they decompose into carbon dioxide, ammonia and alcohols, and when heated with ammonia give urea.

The compound commonly known as *urethane* is the ethyl ester of carbamic acid, $H_2N.CO.OC_2H_5$. It melts at 50° and boils at 184°. When treated with very concentrated nitric acid it yields *nitro-urethane*, $NO_2.NH.CO.OC_2H_5$, from which nitramide was first isolated. Urethane is often employed as a narcotic in physiological experiments on the smaller animals.

Trichloro-ethyl-urethane, $H_2N.CO.OCH_2.CCl_3$, is used as a hypnotic under the name of " Voluntal." Pharmacologically, it stands between chloral and urethane.

Urea, carbamide, $NH_2.CO.NH_2$, the diamide of carbonic acid, was discovered in urine in 1773, and was the first organic substance to be synthesised in the laboratory (Wöhler, 1828). It occurs in the urine of mammals and certain reptiles, and in many other liquids of animal origin. A human adult excretes about 30 gms. of urea per day, as the decomposition product of proteins.

Urea is formed directly by the hydrolysis of egg albumin, serum albumin, casein, gelatin, etc., under the influence of alkali hydroxides, and also, though considerably less rapidly, by use of calcium hydroxide.

Urea can be prepared from urine by boiling down to small bulk and adding nitric acid. Under these conditions urea nitrate is precipitated, from which, after suitable purification, urea can be liberated by means of barium carbonate.

Synthetically, it is obtained by the action of ammonia on phosgene, ethyl carbonate, or urethane. These reactions prove the constitution of urea.[1]

$$\begin{array}{rcl} \begin{matrix} Cl & HNH_2 \\ & C{:}O \\ Cl & HNH_2 \end{matrix} + & = & \begin{matrix} NH_2 \\ C{:}O \\ NH_2 \end{matrix} + 2HCl \\ CO(OC_2H_5)_2+2NH_3 & = & CO(NH_2)_2+2C_2H_5OH \\ CO(NH_2)(OC_2H_5)+NH_3 & = & CO(NH_2)_2+C_2H_5OH \end{array}$$

[1] For an alternative constitution of urea advanced by E. A. Werner see p. 69.

It is also formed by the intramolecular rearrangement of ammonium cyanate, when this is evaporated in aqueous solution [1]:

$$CON.NH_4 \longrightarrow CO(NH_2)_2$$

This is the epoch-making synthesis of urea effected by Wöhler in 1828, by evaporating an aqueous solution of potassium cyanate and ammonium sulphate. The potassium sulphate which crystallised out on cooling was filtered off and the filtrate evaporated to dryness. From the solid residue thus obtained urea can be extracted by means of alcohol.

Urea crystallises in long rhombic prisms or needles, which melt at 132°. It dissolves readily in water and alcohol but is practically insoluble in ether. Acids combine with urea to form salts, the most important being the *nitrate*, CON_2H_4,HNO_3, and oxalate, which are only sparingly soluble in water or nitric acid. Urea may therefore be precipitated from its solutions in these forms. Urea also yields salts with bases, and combines with certain salts to give crystalline addition compounds. Thus mercuric nitrate yields a precipitate of the composition $2CO(NH_2)_2$, $Hg(NO_3)_2$, $3HgO$, on the formation of which is based a volumetric method of estimating urea (Liebig).

Like other acid amides, urea is readily hydrolysed on being heated with dilute acids or alkalis, or with water above 100°. This decomposition also occurs during the putrefaction of urine, $CO(NH_2)_2+H_2O = CO_2+2NH_3$. When heated alone at 150° to 170°, urea parts with ammonia and is converted into **biuret.**

$$NH_2.CO.NH_2+NH_2.CO.NH_2 \longrightarrow \underset{\text{Biuret.}}{NH_2.CO.NH.CO.NH_2}+NH_3$$

Biuret forms colourless needles, melts in the anhydrous state at 190°, and gives a violet coloration with alkali and copper sulphate (see biuret reaction, p. 232). At temperatures above 170° urea yields cyanuric acid. With nitrous acid it reacts to give carbon dioxide, nitrogen and water, $CO(NH_2)_2+N_2O_3 = CO_2+2N_2+2H_2O$. Nitrogen is also liberated by the action of sodium hypochlorite or hypobromite; the complicated reaction which occurs in this case [2] is used in the Hüfner method [3] of estimating urea, by measuring the volume of the nitrogen evolved.

A very convenient and accurate method of estimating urea depends on the action of *urease*, an enzyme occurring in soya beans. This converts urea quantitatively into ammonium carbonate, which can be determined directly by titration, or by liberating the ammonia with potassium carbonate and distilling it over into excess of standard acid.

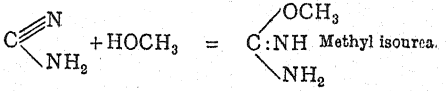
Alkylated ureas, in which hydrogen is replaced by alkyl radicals, are known in considerable number. They are formed by various methods, *e.g.* when primary or secondary amines react with potassium cyanate or isocyanic esters.

$$CO:NR+NH_2CH_3 = NHR.CO.NHCH_3$$

In their properties and reactions they strongly resemble urea.

[1] This process has been shown by J. Walker and Hambly to be a reversible one, *J. C. S.*, 1895, **67**, 746. An *N*/10 aqueous solution of urea at 100° gave about 4 to 5 per cent. of ammonium cyanate. The change was followed by use of silver nitrate, which formed the sparingly soluble silver cyanate. [2] See Schestakow, *C.*, 1905, **I**, 1227. [3] Le Comte, C., 1903, **I**, 1443. Corradia, *C.*, 1906, **I**, 1574. Gracia, *C.*, 1914, **II**, 1, 684.

Alkyl isoureas, $HN:C(OR).NH_2$, derived from an as yet unknown isomeric urea of the formula $HN:C(OH).NH_2$, are obtained by the union of alcohols with cyanamide, under the influence of hydrochloric acid.

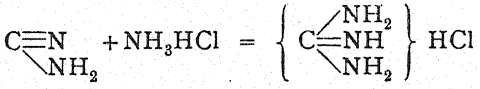


Semicarbazide, $NH_2.CO.NH.NH_2$, is formed by the interaction of potassium cyanate and hydrazine hydrate. It is frequently utilised for the detection and isolation of aldehydes and ketones, since the condensation products, semicarbazones, obtained with these compounds usually crystallise well.

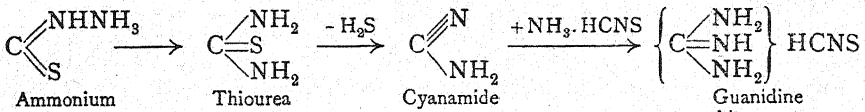
$(CH_3)_2C:O + H_2N.NH.CO.NH_2 \longrightarrow (CH_3)_2C:N.NH.CO.NH_2 + H_2O$

Acetone — Semicarbazide — Acetone semicarbazone.

Guanidine, $NH:C(NH_2)_2$, may be regarded as imino-urea, or as the amidine of carbamic acid. It is contained in the seeds of the vetch and the juice of the sugar-beet, and is formed when cyanamide is heated with ammonium chloride solution.



Guanidine is generally prepared by heating ammonium thiocyanate at 180° to 190°, when cyanamide occurs as an intermediate product.

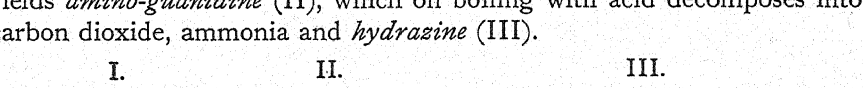


Ammonium thiocyanate — Thiourea — Cyanamide — Guanidine thiocyanate.

It is a strongly basic crystalline compound, which is readily soluble in water and rapidly absorbs carbon dioxide from the air. It combines with one equivalent of acid to form salts, of which the nitrate CH_5N_3, HNO_3, is sparingly soluble in water.

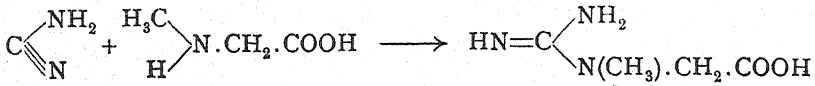
When guanidine is treated with a mixture of nitric and sulphuric acids it is converted into *nitro-guanidine* (I). This is the starting material for the preparation of a number of interesting derivatives of guanidine and urea. On reduction with zinc dust and acetic acid, nitro-guanidine yields *amino-guanidine* (II), which on boiling with acid decomposes into carbon dioxide, ammonia and *hydrazine* (III).

I. II. III.



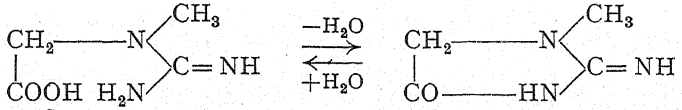
The hydrogen atoms in guanidine can be replaced by alkyl and other radicals. An important substitution product of this type has already been met with in *arginine* (see p. 227). Two other derivatives are creatine and creatinine.

Creatine, *methyl-guanidyl-acetic acid,* was synthesised by Volhard from cyanamide and methylamino-acetic acid (sarcosine).



Creatine.

It was discovered by Chevreul in meat broth, and is present in muscle. Hence it can be prepared from extract of meat. Creatine is a crystalline compound of weak basic properties. It has a bitter saline taste and is soluble in water. When warmed with dilute acids it loses water and yields creatinine.



Creatine Creatinine.

Creatinine is found in urine and in muscle. It is strongly basic and has an alkaline reaction in aqueous solution. By combination with water it may be converted into creatine.

Creatine-phosphoric acid, phosphagen, probably having the structure[1] $HN=C\begin{matrix}NH-PO_3H_2\\ N(CH_3).CH_2.COOH\end{matrix}$, has been shown by Ph. and G. P. Eggleton[2] to be a physiologically important constituent of muscle tissue. It may be regarded as the parent substance of the creatine in the muscle. In the muscles of invertebrates, in which creatine is absent, the place of phosphagen is taken by *arginine-phosphoric acid.*[3] Each of these compounds is characterised by the mobility of the acid amide linking, the phosphoric acid being rapidly and completely removed in the presence of dilute mineral acids, even in the cold.

III.—SULPHUR DERIVATIVES OF CARBONIC ACID

Carbon oxysulphide, COS, is formed by leading a mixture of carbon monoxide and sulphur vapour through a red-hot tube, and by the action of hydrogen sulphide on isocyanic esters: $2OC:N.C_2H_5+H_2S = COS+CO(NH.C_2H_5)_2$. It is a colourless combustible gas of unpleasant odour, which is decomposed slowly by water and rapidly by alkalis to give carbon dioxide and hydrogen sulphide, $COS+H_2O = CO_2+H_2S$.

Carbon subsulphide, C_3S_2, may be prepared by various methods from carbon disulphide. It is a reddish strongly-refracting liquid,[4] which solidifies below 0°.

Carbon disulphide, CS_2, is prepared industrially by leading sulphur vapour over wood charcoal or coke at a red heat, and after fractionation is obtained as a colourless strongly-refracting liquid, b.p. 46° and sp. gr. 1·27. It has an unpleasant smell, a sharp taste, and is very inflammable, burning with a blue flame to give carbon dioxide and sulphur dioxide, $CS_2+3O_2=CO_2+2SO_2$. Carbon disulphide is insoluble in water, but mixes in all proportions with alcohol and ether. It is a good solvent for iodine, sulphur, phosphorus, vegetable oils and resins.

[1] C. Fiske and Subbarow, *Science,* 1927, **65**, 401. [2] Ph. Eggleton and G. P. Eggleton, *Biochem. Journ.,* 1927, **21**, 190. [3] O. Meyerhof and Lohmann, *Biochem. Zeitschr.,* 1928, **196**, 49. [4] *Ber.,* 1912, **45**, 3568.

The following are the more important of its chemical reactions. Chlorine or bromine in the presence of a halogen "carrier" converts it into carbon tetrachloride or tetrabromide. On treatment with an alcoholic solution of potassium hydroxide it forms *potassium xanthate*, which crystallises in brilliant yellow needles :

$$CS_2+KOC_2H_5 = C(OC_2H_5):S(SK)$$

Free *xanthic acids*, of the general formula RO.CS.SH, are very unstable. The name is derived from their property of giving *yellow* precipitates of cuprous xanthates with copper salts.

Carbon disulphide finds a number of uses. Owing to its great solvent power it is employed for extracting sulphur from sulphur ores and coal gas purification residues, and fats and oils from seeds, bones and other materials. It is also the starting material in the manufacture of potassium xanthate (used for destroying the vine louse), carbon tetrachloride, and cellulose xanthates (viscose, pp. 324 and 326).

Thiourea, *thiocarbamide*, $NH_2.CS.NH_2$, is formed from ammonium thiocyanate by an intramolecular change similar to the urea transformation. In this case, however, the reaction takes place less readily (170° to 180°), and is also less complete, owing to the thiourea reverting to thiocyanate.

$$NCS.NH_4 \rightleftharpoons CS(NH_2)_2$$

Thiourea crystallises in rhombic prisms, m.p. 172°, and dissolves readily in water or hot alcohol, but only sparingly in ether or cold alcohol. When boiled with acids or alkalis it decomposes into carbon dioxide, ammonia and hydrogen sulphide $CS(NH_2)_2+2H_2O = CO_2+2NH_3+H_2S$. Oxides of silver, mercury or lead remove hydrogen sulphide, even at the ordinary temperature, and yield cyanamide.

$$CS(NH_2)_2 = NC.NH_2+H_2S$$

Like urea, it is a tautomeric substance,[1] and may react according to either of the formulæ $NH_2.C(NH_2)(=S)$ or $HN:C(NH_2)(SH)$.

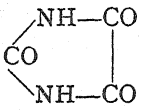
XX

Ureides and Purine Derivatives[2]

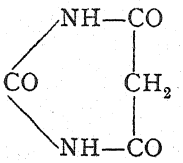
Dibasic acids unite with urea in the same manner as with ammonia, to form compounds of the amide type. When one carboxyl group alone enters into reaction, with loss of one molecule of water, the resulting compounds are known as **ureido-acids.** If both carboxyl groups take part, with elimination of two molecules of water, there are formed cyclic

[1] Werner, *J. C. S.*, 1912, **101**, 1167, 1982, 2116, 2180. [2] E. Fischer, *Ber.*, 1899, **32**, 435. Also "Untersuchungen in der Purin-Gruppe" (Springer, Berlin, 1907).

derivatives of urea known as **ureides.**[1] Of these two groups, the ureides are the more important, as they are closely related to a number of complex products, such as uric acid, which occur in animal and vegetable organisms as a result of protein decomposition. From the typical ureides, oxalyl urea and malonyl urea, can be derived all the members of the uric acid group.



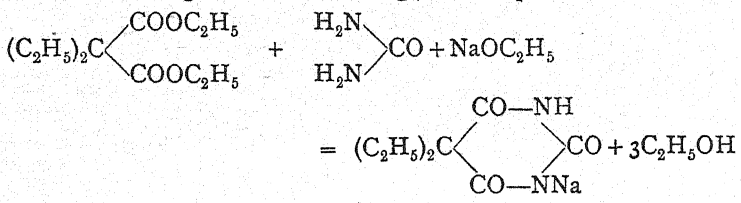
Oxalyl urea
or parabanic acid



Malonyl urea
or barbituric acid.

Malonyl urea is of special interest, as it was from one of its simple derivatives, pseudo-uric acid, that Fischer synthesised uric acid itself. Other derivatives of malonyl urea are dialuric acid (hydroxy-malonyl urea), alloxan (dihydroxy-compound), violuric acid (nitroso-compound), dilituric acid (nitro-compound), and uramil (amino-compound).

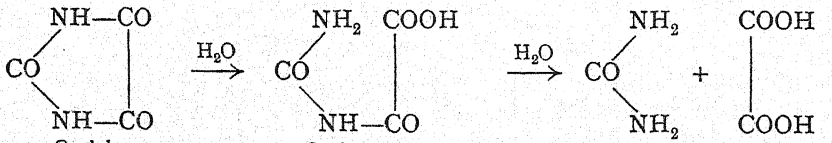
***C*-Diethyl-barbituric acid, veronal,** was isolated in 1882 by Conrad and Guthzeit, by the action of ethyl iodide on the silver salt of barbituric acid. It was not until 1903 that Fischer and Mehring showed that it was an excellent hypnotic. Since then this substance, which is used in medicine under the name of veronal, has become of great interest to the chemical and medical world and has given rise to an extensive scientific and patent literature. Veronal can be prepared by condensing the ester of diethyl-malonic acid with urea in the presence of sodium ethylate, the sodium salt being formed according to the equation



Sodium salt of veronal.

Esters of mono-alkylated malonic acids may also be condensed in the same manner.

The ureides are for the most part beautifully crystalline compounds



Oxalyl urea — Oxaluric acid — Urea — Oxalic acid.

[1] Although these compounds are cyclic, the ring systems are comparatively easily opened. In addition, their properties and methods of formation are so closely related to those of open-chain products that they are more conveniently described at this stage than under the heading of heterocyclic compounds, where they properly belong.

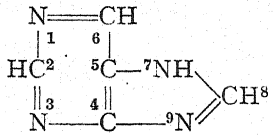
whose character as amides is shown by the fact that on prolonged warming with dilute alkalis they take up two molecules of water to yield a dibasic acid and urea. Ureido-acids occur as intermediate products in this reaction.

Ureides are acidic in character and form salts in which the imido hydrogen is replaced by metals.

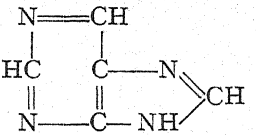
Uric acid and other closely related compounds described here are termed **diureides,** as they contain two urea residues—NH.CO.NH— in the molecule. All are derived from the same parent compound, which Fischer has named **purine.**

The structure of purine may be represented by either of the two following formulæ :

I.



II.



and we are therefore dealing with a case of tautomerism recalling that of the amidines. This peculiarity repeats itself in all those purine derivatives in which no oxygen is present in the five-membered ring. In the following pages formulæ of the type I will be adopted for free purine and all similar compounds.

Purine itself has been obtained from 2 : 6 : 8-trichloro-purine, which is described later. The latter was partially reduced to di-iodopurine by treatment with hydriodic acid and phosphonium iodide at 0°,

$$C_5HN_4Cl_3+4HI = C_5H_2N_4I_2+3HCl+2I$$

and this on reduction with zinc dust and water gave purine. It is a beautifully crystalline substance, m.p. 211° to 212°, which is readily soluble in water and forms salts with both acids and bases.

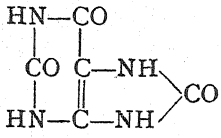
In order to build up a systematic nomenclature for the numerous compounds of this class Fischer numbered the atoms of the purine molecule as in the above formula and denoted the position of substituent groups in the usual manner. Old-established names such as uric acid, xanthine, etc., are, however, still in common use.

The following summary (p. 344) shows the close relationship existing between a number of these compounds.

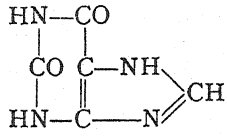
Uric acid, 2 : 6 : 8-*trihydroxy-purine,* $C_5H_4N_4O_3$, was discovered in 1776 by Scheele in urinary calculi and in human urine. Later it was found by Foucroy and Vauquelin in the excrement of birds, and in particularly large quantities (25 per cent.) in the guano of the South Sea Islands. It is also present in the excrement of snakes.

The latter sources consist chiefly of ammonium urate and may be used for the preparation of the acid. Uric acid is a white crystalline powder, very sparingly soluble in hot water, and practically insoluble in cold. As a weak dibasic acid it forms two series of salts, which

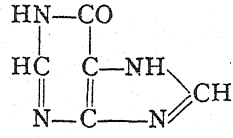
are almost all difficultly soluble. In gouty patients, uric acid separates out in the joints in the form of sparingly soluble acid salts. Water containing lithium salts or piperazine was formerly employed as a remedy, on account of the higher solubility of the urates of lithium and piperazine.



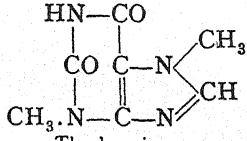
Uric acid,
2 : 6 : 8-trihydroxy-purine



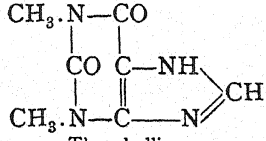
Xanthine,
2 : 6-dihydroxy-purine



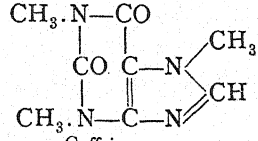
Hypoxanthine,
6-hydroxy-purine.



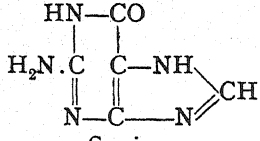
Theobromine,
3 : 7-dimethyl-
2 : 6-dihydroxy-purine



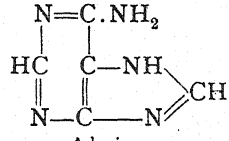
Theophylline,
1 : 3-dimethyl-
2 : 6-dihydroxy-purine



Caffeine,
1 : 3 : 7-trimethyl-
2 : 6-dihydroxy-purine.



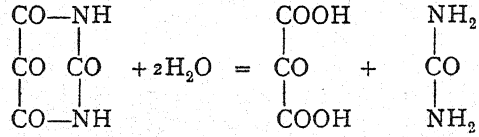
Guanine,
2-amino-6-hydroxy-purine



Adenine,
6-amino-purine.

Reactions of Uric Acid.—Uric acid readily undergoes oxidation; under most conditions the elements of water are also taken up, with the elimination of first one urea residue and finally the second.

1. By moderate oxidation with nitric acid, uric acid yields urea and **alloxan**; consequently the atomic framework of the latter compound must be present in uric acid. The constitution of alloxan as *mesoxalyl urea* follows from its decomposition with alkalis.



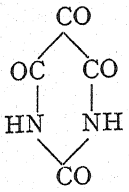
Alloxan Mesoxalic acid Urea.

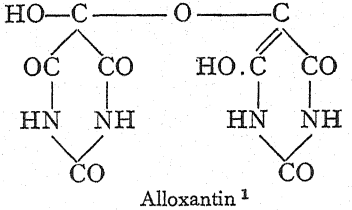
By more energetic treatment with nitric acid the alloxan first produced is converted into *parabanic acid* or *oxalyl urea* (see p. 342), together with carbon dioxide and ammonia.

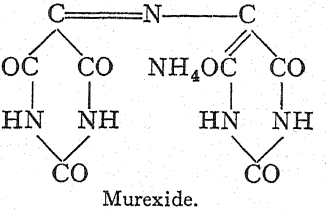
With reducing agents alloxan yields alloxantin, which, with ammonia, gives *murexide*, the ammonium salt of purpuric acid. Murexide crystallises in greenish gold prisms and dissolves in water to a purple solution. It may be used for the identification of uric acid and urates, since alloxantin is also formed directly from uric acid by evaporation with dilute nitric acid.

The *murexide test* is carried out by adding a little dilute nitric acid to a few crystals

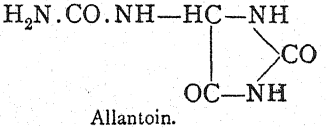
of uric acid and carefully evaporating to dryness. The red residue becomes purple on the addition of ammonia, and blue with caustic soda.


Alloxan


Alloxantin [1]

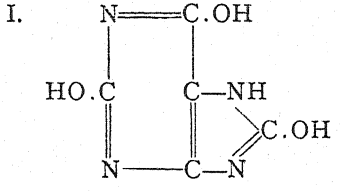

Murexide.

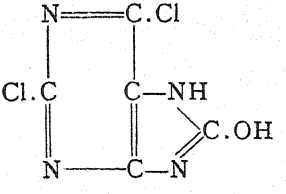
2. The oxidation of uric acid with alkaline permanganate leads through several intermediate products to the formation of **allantoin,**[2] so that the five-membered ring of this compound must also be contained in uric acid. The formulation of allantoin as a ureide of glyoxalic acid, having the structure

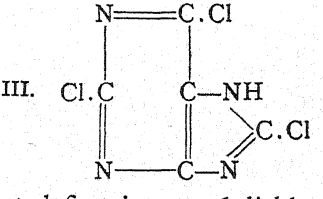

Allantoin.

is based on its synthesis from glyoxalic acid and urea at 100°.

The reactions quoted under 1 and 2 confirm the above formula for uric acid, which was first put forward by Medicus on general grounds, and later established by E. Fischer [3] by his investigations on the methyl derivatives of uric acid and by synthesis. Before describing the synthesis of uric acid, the behaviour of the compound towards phosphorus oxychloride may be noted. With this substance it reacts in the tautomeric


I.


II.

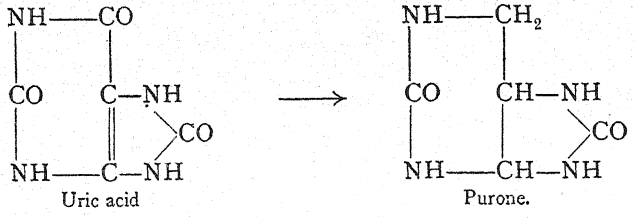

III.

form (I), being converted first into 2 : 6-dichloro-8-hydroxy-purine (II), and finally into 2 : 6 : 8-trichloro-purine (III). These chloro-compounds,

[1] O. Piloty, *Ann.*, 1904, **333**, 22. For objections against the above formula see Möhlau, *Ber.*, 1904, **37**, 2686; Slimmer and Stieglitz, *Am. C. J.*, 1904, **31**, 661. [2] *Allantoin*, m.p. 238° to 240°, occurs in the urine, especially of carnivorous animals, and is widely distributed in the vegetable kingdom. In many animals it is eliminated in the urine as the end-product of nitrogen metabolism, thus playing a similar rôle to uric acid in the human organism. It crystallises in prisms which are sparingly soluble in cold water. [3] E. Fischer, *Ann.*, **175**, 243.

and particularly 2 : 6 : 8-trichloro-purine, are of great importance for the synthesis of other purine derivatives from the comparatively cheap uric acid. The chlorine atoms are very reactive, and can readily be exchanged for the groups C_2H_5O—, HO—, HS—, H_2N—, I—, and also in part by hydrogen.[1] In this way it is possible to obtain a large variety of derivatives in addition to naturally occurring products. Synthesis has far outstripped nature in this respect. Physiology and medical practice have derived great benefit from these investigations. Owing to their medicinal value, *caffeine*, *theobromine* and *theophylline* are now prepared industrially by Fischer's method from the uric acid of guano.

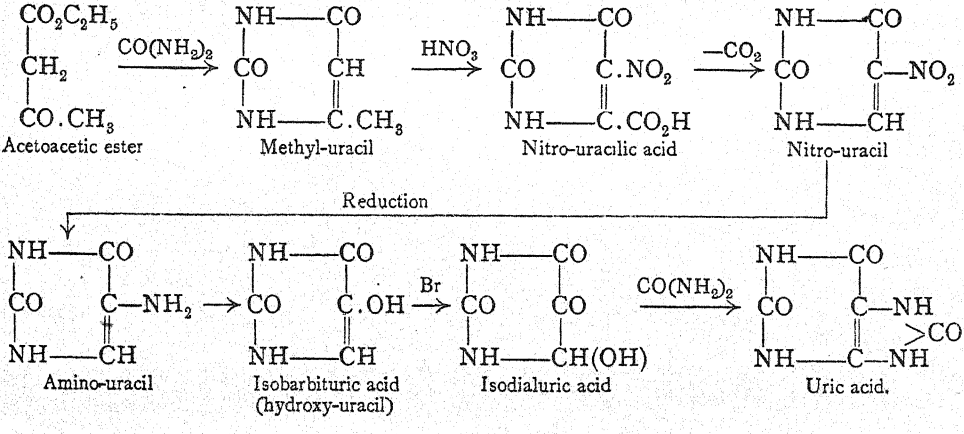
The *electrolytic reduction of uric acid* proceeds according to the equation $C_5H_4O_3N_4+6H=C_5H_8O_2N_4+H_2O$, yielding a product known as *purone*.[2]



Uric acid — Purone.

Acidity of the Hydrogen Atoms in Uric Acid.—It has been established [3] that the hydrogen atom in position 3 is the most strongly acidic. Its replacement by metals leads to the formation of acid salts. The atom in position 9 is next in acidic strength, and neutral urates are formed by replacement of these two atoms.

Synthesis of Uric Acid.—1. The first decisive synthesis of uric acid was effected in 1889 by Behrend and Roosen,[4] in the following stages.

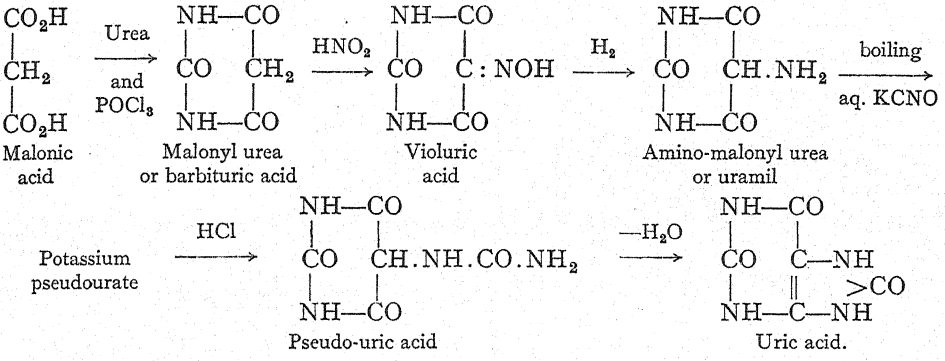


Acetoacetic ester — Methyl-uracil — Nitro-uracilic acid — Nitro-uracil

Amino-uracil — Isobarbituric acid (hydroxy-uracil) — Isodialuric acid — Uric acid.

[1] E. Fischer, Ber., 1899, **32**, 445. [2] Tafel, *Ber.*, 1901, **34**, 261, 1181. [3] Biltz and Herrmann, *Ber.*, 1921, **54**, 1676. [4] *Ann.*, 1889, **251**, 235.

2. The next and simplest synthesis of uric acid was carried out by Fischer and Ach in 1895.[1] This depends on the removal of the elements of water from pseudo-uric acid by fusion with oxalic acid, or more conveniently by boiling with strong hydrochloric acid. Pseudo-uric acid was prepared from malonic acid in the following manner :

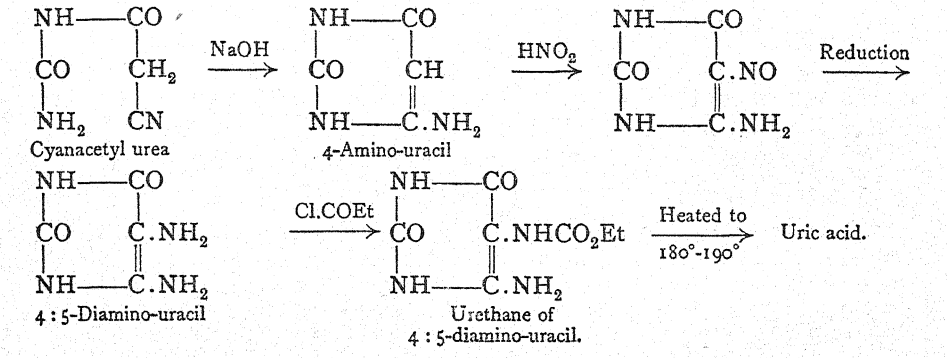


As violuric acid is the oxime of alloxan, this synthesis permits the reconstruction of the uric acid molecule from its chief oxidation product, alloxan. Further, by starting from methyl alloxan and dimethyl alloxan there can be obtained methyl pseudo-uric acids, from which it is possible to prepare methylated uric acids.

3. A synthesis of general application and hence of great preparative value is that due to Traube. It makes use of cyanacetyl urea,[2] formed by condensing cyanacetic acid with urea (formula below).

By utilising the alkyl derivatives of urea this synthesis may be employed for the preparation of alkylated uric acids.

A compound very closely related to uric acid is **xanthine,** or 2 : 6-*dihydroxy-purine* (formula p. 344), which may be obtained synthetically by Fischer's[3] method from 2 : 6 : 8-trichloro-purine, or by Traube's



method,[4] from cyanacetyl-urea. Trichloro-purine on treatment with sodium ethoxide is converted into 2 : 6-diethoxy-8-chloro-purine, and

[1] *Ber.*, 1895, **28**, 2473. [2] W. Traube, *Ber.*, 1900, **33**, 3035. [3] *Ber.*, 1897, **30**, 2235; *Ber.*, 1899, **32**, 468. [4] *Ber.*, 1900, **33**, 3035; *Ann.*, 1904, **331**, 64. For the preparation of xanthine see H. Biltz and A. Beck, *J. prakt. Chem.*, 1928 [2], **118**, 166.

this with hydriodic acid yields xanthine, the ethoxy groups undergoing hydrolysis and chlorine being replaced by hydrogen. Xanthine is a normal constituent of many animal tissues. It is an amorphous powder which is very sparingly soluble in water. On electrolytic reduction it yields *desoxy-xanthine*,[1]

$$C_5H_4O_2N_4+4H = C_5H_6ON_4+H_2O.$$

The most important of the five naturally occurring methyl derivatives [2] of xanthine is **caffeine**, 1 : 3 : *7-trimethyl-2 : 6-dihydroxy-purine* (formula p. 344).

It occurs in the leaves and beans of the coffee tree (1·2 per cent.), in tea (2 to 4 per cent.), and in kola nuts (3 per cent.). It also occurs in small amounts in cocoa. It crystallises in silky needles containing 1 molecule of water, which is partly lost in air at ordinary temperatures and completely driven off at 100°. Caffeine melts at 234·5°, and on electrolytic reduction is converted into desoxy-caffeine.[3]

Caffeine is the component of tea and coffee responsible for the stimulating action of these beverages on the nerves and heart. For this reason it is employed in medicine.

Originally the bulk of the caffeine used was prepared from tea dust. Nowadays it is prepared by other methods, *e.g.* from uric acid.

Caffeine from Uric Acid.—When uric acid is shaken in aqueous alkaline solution with methyl iodide, its four hydrogen atoms are replaced by four methyl groups with the production of tetramethyl-uric acid. This on being heated with phosphorus oxychloride yields chloro-caffeine, in which reaction the methyl group in position 9 becomes detached, and the oxygen in position 8 replaced by chlorine. Finally, the chloro-caffeine is reduced to caffeine.[4] An industrial process for the manufacture of caffeine takes place in the following stages: Uric acid ⟶ 8-methyl-xanthine ⟶ 1:3:7:8-tetramethyl-xanthine ⟶ 1:3:7-trimethyl-8-trichloromethyl-xanthine ⟶ caffeine.

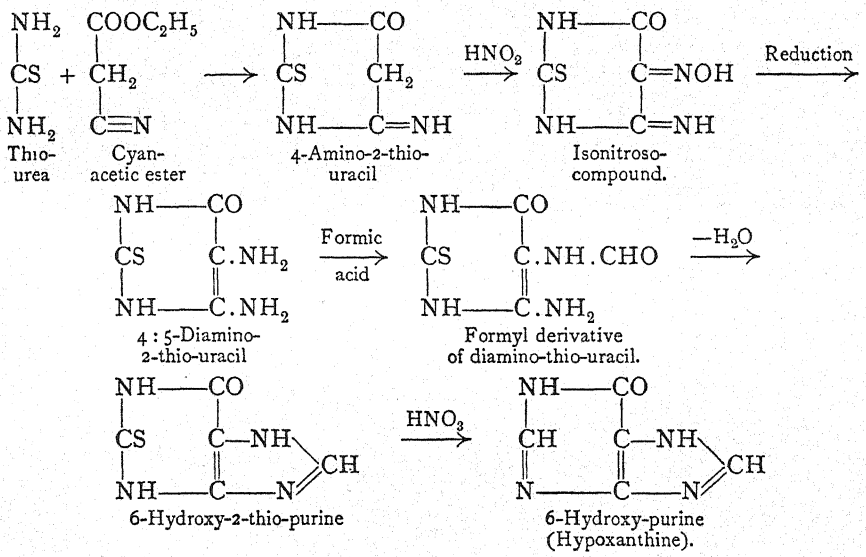
A compound closely related to caffeine is **theobromine**, 3 : *7-dimethyl-2 : 6-dihydroxy-purine* (formula p. 344), which occurs in cocoa (1 to 2 per cent.). It is a white crystalline powder which sublimes unchanged at about 290° and is employed as a diuretic. Its structure has been shown by synthesis from 3 : 7-dimethyl-uric acid.[5]

Theophylline, 1 : *3-dimethyl-2 : 6-dihydroxy-purine* (formula p. 344) is isomeric with theobromine and has been found in tea. The anhydrous

[1] Tafel and Ach., *Ber.*, 1901, **34**, 1165. [2] Substituent methyl groups exert a very considerable influence on the properties of purine derivatives. In general, the entrance of methyl groups increases the solubility in water and lowers the melting-point. This is well illustrated by the differences in solubility shown by xanthine, theobromine and caffeine. Further, the volatility (ease of sublimation) is also increased by methylation. Methyl derivatives usually crystallise better than the parent compounds, and are therefore sometimes of value in identifying the latter. The transformation of pseudo-uric acid into uric acid is effected more readily with the methyl derivatives, and is specially promoted by the introduction of a methyl group into the 7-position. Finally, the fission of the purine nucleus is influenced to a marked degree by methylation, and takes place far more readily in the case of those derivatives in which the acidic hydrogen has been totally replaced by alkyl groups. [3] Tafel and Baillie, *Ber.*, 1899, **32**, 3206. [4] E. Fischer, *Ber.*, 1897, **30**, 3010. [5] E. Fischer, *Ber.*, 1897, **30**, 1839.

compound melts at 264°, and in its diuretic action surpasses theobromine. It was the first xanthine derivative to be prepared artificially, being obtained from 1 : 3-dimethyl-uric acid.[1] The latter compound on treatment with a mixture of phosphorus oxychloride and pentachloride gave chloro-theophylline, which was then reduced to theophylline. On the technical scale it is prepared from symmetrical dimethyl urea and cyanacetic acid.[2] Another industrial method of preparation is analogous to that indicated above for caffeine, with the difference that 8-trichloromethyl-caffeine (1 : 3 : 7-trimethyl-8-trichloromethyl-xanthine) is transformed by further chlorination into 1 : 3-dimethyl-7-chloromethyl-8-trichloromethyl-xanthine. This on hydrolysis yields theophylline. It is used as a diuretic.

Hypoxanthine, or *sarkine*, 6-*hydroxy-purine* (formula p. 344), is frequently found associated with xanthine in the animal organism, and is consequently present in extract of muscle, spleen and liver. It is a crystalline powder of basic character, which decomposes at 150°. It may be prepared from 2 : 6 : 8-trichloro-purine,[3] which on being heated with alkalis yields 6-hydroxy-2 : 8-dichloro-purine. The latter on reduction with hydriodic acid is converted into hypoxanthine. It has also been synthesised from cyanacetic ester and thiourea [4] in the following stages :



Whereas the hydroxy-purines, *uric acid*, *hypoxanthine* and *xanthine* are formed in the animal organism as intermediate or final products of metabolism with a view to subsequent elimination from the system, the following amino-purines, *guanine* and *adenine*, are essential constituents of the important nucleic acids and must be regarded as indispensable for the life processes of the cell.

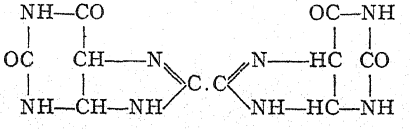
[1] Fischer and Ach, *Ber.*, 1895, **28**, 3135. [2] W. Traube, *Ber.*, 1900, **33**, 3041. [3] E. Fischer, *Ber.*, 1897, **30**, 2226. [4] W. Traube, *Ann.*, 1904, **331**, 67.

Guanine, *2-amino-6-hydroxy-purine* (formula p. 344), occurs in the pancreas of certain animals and is present in large amounts in guano. It may be obtained from 6-hydroxy-2 : 8-dichloro-purine (dichloro-hypoxanthine) by heating with alcoholic ammonia, and reducing the chloro-guanine so formed with hydriodic acid [1]; it is more readily prepared from cyanacetic ester and guanidine.[2] When treated with nitrous acid it is converted into 2 : 6-dihydroxy-purine or xanthine.

Adenine, *6-amino-purine* (formula p. 344), is formed together with xanthine, hypoxanthine and guanine when *nuclein*, the chief constituent of the cell nucleus, is boiled with dilute acids. It has been synthesised by the action of ammonia on trichloro-purine, and reduction of the 6-amino-2 : 8-dichloro-purine thus obtained.[3] Like hypoxanthine, it may also be prepared from sulphur compounds; the starting materials in this case are thiourea and the nitrile of cyanacetic acid. When treated with nitrous acid, adenine is converted into 6-hydroxy-purine or hypoxanthine.

Recent investigations indicate that the colouring matters of butterflies' wings are also to be classed as purine derivatives. Wieland proposes to name these pigments *lepidopterins* or *pterins*.

Xanthopterin,[4] $(C_5H_5O_2N_4)_2$, the yellow pigment of the lemon butterfly, *Gonepteryx rhamni*, was obtained from the ammonium salt as a yellow amorphous powder. After purification by way of the barium salt it formed orange-brown globular aggregates, probably of the following structure :



Leucopterin,[5] probably of the composition $C_{19}H_{19}O_{11}N_{15}$, is the pigment present in the wings of the white butterfly.

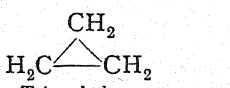
[1] E. Fischer, *Ber.*, 1897, **30**, 2251. [2] W. Traube, *Ber.*, 1900, **33**, 1371. [3] E. Fischer, *Ber.*, 1897, **30**, 2238. [4] H. Wieland and C. Schöpf, *Ber.*, 1925, **58**, 2178. [5] Wieland, Metzger, Schöpf and Bülow, *Ann.*, 1933, **507**, 226.

PART II

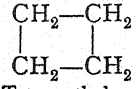
Chemistry of the Carbocyclic Compounds

As already stated on p. 16, compounds containing open chains are classed as aliphatic, and those containing closed chains or rings as cyclic. The following section deals with those cyclic compounds in which the rings are built up entirely of carbon atoms, and which are therefore most conveniently grouped under the heading *carbocyclic*.[1]

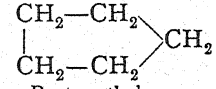
Included in this group are certain hydrocarbons having the same composition, C_nH_{2n}, as the homologues of ethylene, although possessing very different properties. These hydrocarbons are termed poly-methylenes, or, according to the Geneva nomenclature, are named by prefixing *cyclo* to the names of the corresponding normal paraffins :



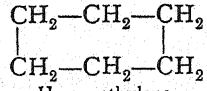
Trimethylene, Cyclopropane



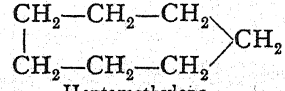
Tetramethylene, Cyclobutane



Pentamethylene, Cyclopentane



Hexamethylene, Cyclohexane



Heptamethylene, Cycloheptane.

Some of these compounds give rise to large numbers of derivatives.

Of far greater interest than these hydrocarbons and their derivatives, which are often described as *alicyclic* compounds, is the large and important class made up of the true *aromatic* compounds related to benzene, C_6H_6. Before discussing the latter in detail a brief survey of the other groups will be given.

I

Tri-, Tetra-, Penta- and Heptamethylene Compounds and the Cyclo-olefins

Some of the more important cycloparaffins and their physical constants are listed in the following table. It may be noted that the energy contents indicated by the last column are in agreement with Baeyer's strain theory as modified by the work of Ruzicka (see p. 357), rings larger than cyclobutane being apparently without strain.

Alicyclic compounds occur widely in nature, the majority of them containing 5- or 6-membered rings. Examples of this type are the naphthenes present in petroleum, which are hydrocarbons of the cyclopentane

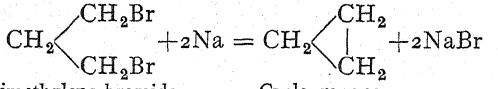
[1] These are sometimes called homocyclic or isocyclic compounds.

and cyclohexane series; the naphthenic acids, also found in petroleum; and the essential oils or terpenes, which are treated in more detail in connection with the aromatic compounds.

	Formula.	B.p.	M.p.	d_4°	Heat of Combustion in Cal. per CH_2.
Cyclopropane . .	C_3H_6	-35°	-127°	—	168·5
Cyclobutane . .	C_4H_8	$+12^{\circ}$	...	0·7038	165·5
Cyclopentane . .	C_5H_{10}	49°	...	0·7635	159
Cyclohexane . .	C_6H_{12}	81°	$+7^{\circ}$	0·7934	158
Cycloheptane . .	C_7H_{14}	117°	-12°	0·8252	158
Cyclooctane . .	C_8H_{16}	148°	$+11·5^{\circ}$	0·850	...
Cyclononane . .	C_9H_{18}	172°	...	0·785	...
Cyclodecane . .	$C_{10}H_{20}$	201°	$+9·6^{\circ}$	...	158·6

Preparation.—Compounds of this group may be synthesised by a great variety of reactions, only the more important of which can be dealt with here.

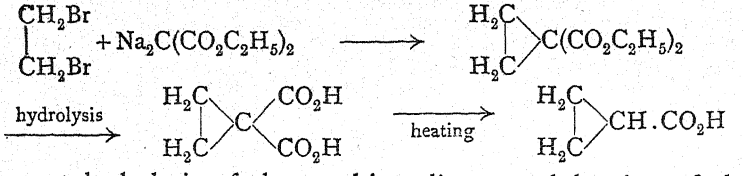
(1) Hydrocarbons can be prepared by the Wurtz reaction, by treating the corresponding dibromoparaffins with sodium, *e.g.*



Trimethylene bromide Cyclopropane.

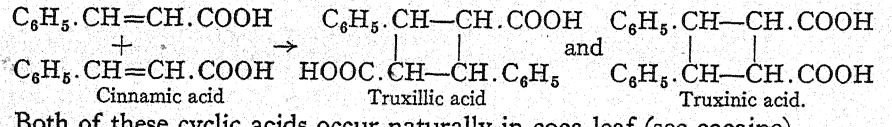
This method gives very good yields of cyclopropane derivatives, but with higher homologues various side-reactions occur.

(2) By Perkin's method from sodio-malonic ester and ethylene bromide, trimethylene bromide or tetramethylene bromide. The elimination of halogen takes place in two stages and not in the abbreviated form shown in the following scheme.



Subsequent hydrolysis of the resulting diester and heating of the dicarboxylic acid yields a mono-carboxylic derivative. The final yields agree closely with the expectation based on Baeyer's strain theory, the highest being in the cyclopentane group and the lowest in the cyclopropane group.

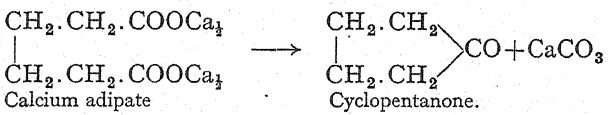
(3) By the condensation of unsaturated compounds. Thus cinnamic acid under the influence of light slowly polymerises to truxillic and truxinic acids.



Cinnamic acid Truxillic acid Truxinic acid.

Both of these cyclic acids occur naturally in coca-leaf (see cocaine).

(4) Cyclic ketones are formed by the dry distillation of calcium salts of certain higher dicarboxylic acids of the oxalic acid series.

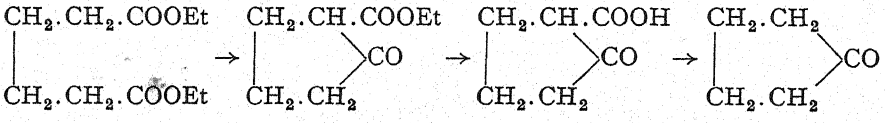


Calcium adipate — Cyclopentanone.

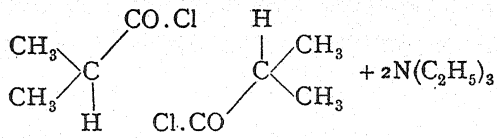
No 3-membered and few 4-membered rings can be synthesised by this method. Ruzicka has shown that with pimelic and higher acids greatly increased yields of cyclic ketones are obtained by use of the thorium salts.

A modification of the above reaction due to Blanc is to submit the anhydride of the acid to slow distillation (compare structure of the bile acids, p. 589). In this case the contraction of the ring by loss of carbon dioxide is greatly facilitated by the presence of alkyl substituents in the α or β positions to the carboxyl group.

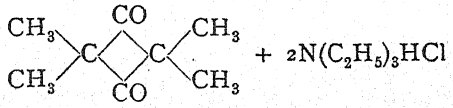
(5) By Dieckmann's method in which an appropriate dicarboxylic ester is treated with sodium to undergo an intramolecular acetoacetic ester condensation, *e.g.* with adipic ester,



(6) Among diketones of the cyclobutane series the first representative to be prepared was tetramethyl-cyclobutane-dione. This was obtained by the action of triethylamine on isobutyryl chloride.[1]

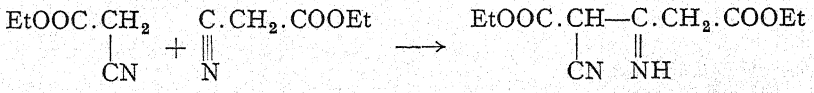


2 Mols. isobutyryl chloride



2 : 2 : 4 : 4-Tetramethyl-cyclobutan-dione-1 : 3.

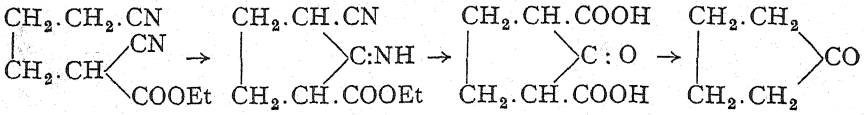
(7) By Thorpe's reaction in which nitriles undergo condensation in the presence of sodium ethoxide to yield cyclic ketones. The mechanism of this reaction may be illustrated by the case of cyanacetic ester, two molecules of which react as follows :



Using $\alpha\delta$-dicyanovaleric ester this reaction leads to the formation of

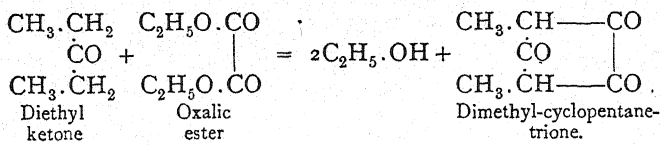
[1] Wedekind, *Ber.*, 1906, **39**, 1631 ; 1911, **44**, 3285. For the formation and rupture of 4-membered rings see also Staudinger, *Ber.*, 1911, **44**, 521.

cyclopentanone dicarboxylic acid, from which cyclopentanone is obtained by loss of carbon dioxide.



This process has been adapted with great success to the synthesis of large ring compounds [1] by condensing alkylene dicyanides, $NC.CH_2(CH_2)_nCH_2.CN$, in the presence of lithium amides, $LiNR_2$. These reactions must be carried out using the cyanides in high dilution in order that intramolecular and not intermolecular condensation shall predominate. Yields of the order of 40 per cent. have been obtained.

(8) A modification of Dieckmann's method (see 5), due to Claisen, involves the condensation of substituted acetones with oxalic ester, when two molecules of alcohol are eliminated and cyclopentane-triones formed.[2]



Up to the present it has not been found possible to use this reaction with acetone itself.

General Properties.—In spite of the similarity in structure between the cycloparaffins and their derivatives and true aromatic compounds, these two series show very considerable differences in chemical behaviour, the former approximating in properties to the aliphatic series.

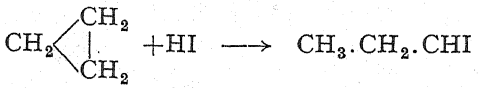
On examining the physical properties of saturated compounds containing closed chains it is seen that these possess higher boiling-points and higher specific gravities than the isomeric unsaturated aliphatic compounds, and also than the saturated aliphatic compounds containing an additional two atoms of hydrogen. This may be illustrated by the following figures: cyclohexane, C_6H_{12}, b.p. 81°; *n*-hexane, C_6H_{14}, b.p. 69°; *n*-hexylene-1, C_6H_{12}, b.p. 68°. Considerable differences are also visible on comparing the magnetic rotations of saturated ring compounds with those of the corresponding unsaturated compounds having open chains. Thus the magnetic rotation of cyclohexane, C_6H_{12}, is 5·664, and that of hexylene or methylpropyl-ethylene, C_6H_{12}, is 7·473.

As has already been stated, the most important group of alicyclic compounds, known as the terpenes or essential oils, is dealt with later. A brief description is given here of some of the simple hydrocarbons and their derivatives.

Cyclopropane, C_3H_6, is prepared by treating 1 : 3-dibromopropane with sodium. It is a gas (b.p. −35°) which is used to some extent as an anæsthetic. The strain in the 3-membered ring is illustrated by the ease

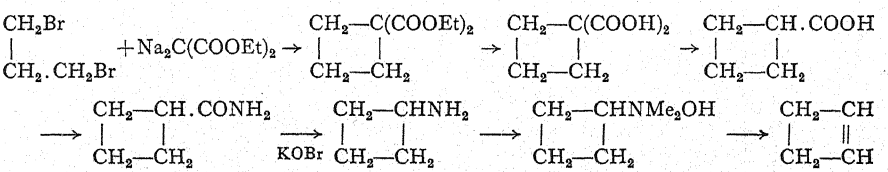
[1] Ziegler, Eberle and Ohlinger, *Ann.*, 1933, **504**, 94. [2] Claisen and Ewan, *Ann.*, 1894, **284**, 247. Diels, *Ber.*, 1906, **39**, 1328.

with which it is ruptured to form open-chain derivatives. Thus cyclopropane reacts readily with hydrogen iodide to yield iodopropane. With



bromine in sunlight it is converted comparatively rapidly into 1 : 3-dibromopropane ; with hydrogen and colloidal palladium in acetic acid solution propane is formed. Under the influence of heat, especially in the presence of a catalyst such as iron filings or platinum, the ring is opened with the formation of propylene, $CH_3.CH : CH_2$. On the other hand, cyclopropane is not attacked by cold potassium permanganate solution, nor by ozone.

Cyclobutane, C_4H_8, is a liquid boiling at +12°. It was prepared by Willstätter through the intermediate compound *cyclobutene*, which was obtained by distilling the quaternary ammonium hydroxide of aminocyclobutane. Starting from trimethylene bromide and sodiomalonic ester, the process involved the following steps :



On reducing cyclobutene catalytically [1] with hydrogen and nickel at 100° pure cyclobutane was obtained. If the reduction is carried out at the more usual temperature of 180-200°, the ring is ruptured and the product is butane. Cyclobutane is not attacked by hydriodic acid or by permanganate in the cold.

Cyclopentane, C_5H_{10}, b.p. 49°, may be prepared from 1 : 5-dibromopentane and zinc, or by reduction of the easily accessible *cyclopentanone*. It occurs naturally in the naphthenes present in Caucasian and American petroleum.

Cyclopentane is unaffected by bromine in the dark, but in light it undergoes normal substitution to form *bromocyclopentane*. The latter is converted into the unsaturated compound cyclopentene on treatment with alcoholic potash. The cyclopentane ring is not opened by catalytic hydrogenation with nickel below 300°.

Zelinsky [2] has observed that when 1-methyl-3-cyclopentanone is led over nickel at 250° it yields methyl-cyclopentane, b.p. 72°. This is a convenient method of preparing the compound. No rupture of the ring occurs in this reaction, despite the comparatively high temperature and presence of nickel catalyst.

For **cyclohexane** and its derivatives see p. 469 *et seq.*

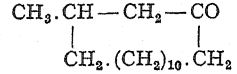
[1] Willstätter and Bruce, *Ber.*, 1907, 40, 3979. [2] *Ber.*, 1911, 44, 2781 ; 1926, 59, 2580.

Cyclo-octanone is an example of a cyclo-octane derivative. It is formed in small amounts (5 per cent.) when the calcium salt of azelaic acid is distilled. According to Ruzicka,[1] yields of 25 per cent. may be obtained by distilling the thorium salt.

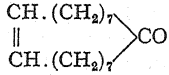
Cyclo-nonanone is obtained in small yield by the dry distillation of thorium sebacate. It boils at 95° to 97° under a pressure of 17 to 18 mm. When reduced in boiling alcoholic solution with metallic sodium it yields cyclo-nonane. (See table on p. 352.)

Monocyclic ketones containing 16, 18 and 30 carbon atoms respectively in the ring have also been synthesised.[2]

Naturally occurring compounds of this type are the powerfully odorous ketones **muscone** (from the musk deer) and **civetone** (from the civet cat). **Muscone**, $C_{16}H_{30}O$,



Muscone



Civetone.

is a saturated optically active liquid, which has been shown by Ruzicka to contain a 15-membered ring. **Civetone**, $C_{17}H_{30}O$, melts at 31°. It is a symmetrical unsaturated ketone which yields azelaic acid on oxidation.

The Relative Stability and Ease of Formation of Ring Compounds (Baeyer's Strain Theory)

A striking point which emerges from a closer examination of the above-mentioned ring systems is the difference in their stability and in the relative ease with which they are formed. Baeyer explained this in his **strain theory** as follows :—

According to the fundamental hypothesis of stereochemistry, the four affinities of a carbon atom act in the direction of lines which may be imagined to be drawn from the central point of a tetrahedron to its summits, and thus make an angle of 109° 28′ with each other. If, however, carbon atoms unite together to form a closed chain these affinities become diverted from their natural directions, and a strain is set up which may be measured by the angle of displacement. As may easily be seen, this tension is least in the five-membered rings. Rings possessing a smaller or greater number of carbon atoms than the pentamethylene ring are under greater tension than the latter. The magnitude of the tension in any individual case is readily calculated. In the trimethylene ring, for example, the carbon atoms may be imagined to be at the corners of an equilateral triangle. The bonds joining them thus enclose angles of 60°, and the distortion of each bond is therefore $\frac{1}{2}$ (109° 28′—60°)= 24° 44′. The following summary gives the values for the distortion in the formation of different polymethylene rings :

(Double bond)	Tri-	Tetra-	Penta-	Hexa-	Hepta-
+54° 44′	+24° 44′	+9° 34′	+0° 44′	−5° 16′	−9° 33′

From these figures it follows that the cyclopentane ring is under the least strain and should therefore be the most stable. In the remaining systems, on the other hand, the valency bonds tend, in varying degree, to assume their original positions in space and therefore to open up the ring. In the case of the above rings these theoretical deductions have

[1] *Helv. chim. Acta*, 1926, 9, 339, *et seq.* [2] *Helv. chim. Acta*, 1928, 11, 496.

been largely confirmed by experiment. In ethylene the strain is greatest, and hence the tendency to form addition compounds, with the simultaneous opening of the ring, is at its highest. This shows itself in the extraordinary speed with which ethylene adds on chlorine, bromine or hydrobromic acid. The distortion is far less in the case of cyclopropane, and consequently the opening of the ring by addition of bromine or hydrobromic acid is effected much less readily than in the case of ethylene. Nevertheless, addition does occur, especially under the influence of light and in the presence of a peroxide.[1] The cyclobutane ring, again, is more stable than the cyclopropane ring, as is readily seen on comparing certain derivatives of these two hydrocarbons. Cyclopropane carboxylic acid, for example, is easily attacked by hydrobromic acid, whereas cyclobutane carboxylic acid under the same conditions is scarcely affected. Finally, cyclopentane and cyclohexane carboxylic acids are unchanged even on prolonged boiling with hydrobromic acid.

Further confirmation of the validity of the strain theory is also found in the heats of combustion of compounds containing saturated 3-, 4-, 5- and 6-carbon rings,[2] as may be seen in the table on p. 352.

An interesting development of stereochemical theory may often be observed in the properties of a homologous series, *i.e.* of a series of compounds containing a *growing chain*. When the latter contains 5 or 6 carbon atoms (or 10, 11, etc.) the properties of the corresponding compounds often deviate from those of the preceding and succeeding members of the series. This is due to the fact that a chain of this length will tend to return on itself, thus subjecting a group in the neighbourhood of atom 1 to an abnormal influence. Such abnormalities have been noted in connection with optical activity (Frankland, Pickard and Kenyon), acid strength and various other properties. *Hexyl resorcinol* (caprokol), for example, has been found to be the most effective internal antiseptic out of a number of homologous derivatives (see p. 429).

As has recently been shown by Ruzicka, the conditions may be quite otherwise in the case of rings containing a large number of carbon atoms. Although not readily prepared, such compounds possess a high degree of stability, and it appears that, by virtue of its magnitude, the ring is able to crumple up or twist itself into positions in which there is little or no distortion of the carbon bonds and hence no strain. Naturally occurring substances of this type are the strongly odorous ketones *muscone* and *civetone*, having 15- and 17-membered rings respectively (see p. 356).[3] For rings containing more than 20 carbon atoms it is probable that the arrangement in the solid is one of double parallel chains,[3] the straight portions of which have a structure identical with that of the normal paraffins.

A later development from Baeyer's strain theory, which has contributed greatly to our knowledge of condensed ring systems of aliphatic type, is the *Sachse-Mohr theory of strainless rings*. This is dealt with on p. 545 *et seq.*

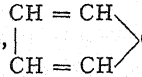
[1] Kharasch, Fineman and Mayo, *J. A. C. S.*, 1939, **61**, 2139. [2] *J. pr. Ch.*, 1892 [2], **45**, 489. See, however, Ingold, *J. C. S.*, 1921, **119**, 305. [3] Ruzicka, *Helv. chim. Acta*, 1926, **9**, 339. *Chem. and Ind.*, 1935, **54**, 2.

CYCLO-OLEFINS

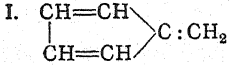
The cyclo-olefins bear the same relationship to the cycloparaffins as the olefins to the paraffins. The simplest representative cyclopropene is unknown, and although *cyclobutene* has been prepared the doubly unsaturated cyclobutadiene has never been isolated. All attempts to remove hydrogen bromide from 1 : 2-dibromo-cyclobutane (I) by use of potassium hydroxide have led either to the formation of bromo-cyclobutene (II) or of acetylene. Treatment with quinoline converts the dibromocyclobutane into butadiene (III) and other products.

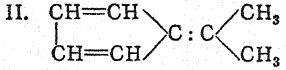
I. CH_2—$CHBr$ / CH_2—$CHBr$ II. CH_2—CH / CH_2—CBr III. CH_2=CH / CH_2=CH

Thiele's partial valency theory clearly does not apply in this case, since the conjugated double bonds in the cyclobutadiene system are not stabilised.

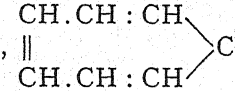
Cyclopentadiene,  , is a colourless liquid, b.p. 41°, which is obtained in the first runnings of the crude benzene from coal tar. It readily polymerises, and at temperatures up to 100° yields chiefly dicyclopentadiene, $C_{10}H_{12}$. Above this, *e.g.* at 135°, polycyclopentadienes $(C_5H_6)_n$ are also formed.

In cyclopentadiene the two hydrogen atoms of the CH_2 group are very reactive, owing to the proximity of the two double bonds; one of them, for example, may be replaced by potassium. Further, under the influence of sodium hydroxide or ethoxide, cyclopentadiene condenses with aldehydes and ketones, the CH_2 group of the former reacting with the C : O group of the latter with elimination of water. The resulting condensation products, of which that with acetone possesses the structure II, have an intense orange to blood-red colour, and may be represented as substitution products of an isomeride of benzene having the formula I. Thiele calls this unknown hydrocarbon **fulvene.**

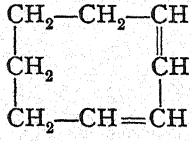
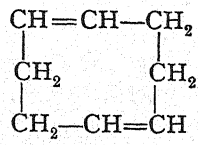
I.  Fulvene

II.  Dimethyl-fulvene.

The fulvenes provide an interesting illustration of the manner in which the colour of an organic compound is influenced by the presence and arrangement of double bonds within the molecule.[1]

Cycloheptatriene, *tropilidene,*  , is a degradation product of the alkaloids cocaine and atropine, and can be prepared from suberone.[2] It is a liquid, b.p. 116°, which smells of leeks.

Cyclo-octadiene (I) has been obtained by the exhaustive methylation (see p. 686) of pseudo-pelletierine,[3] an alkaloid found in the pomegranate.

I.  II. 

It boils at 39·5° under 16·5 mm. pressure, and possesses a penetrating and nauseous smell. It polymerises very readily (explosively on heating)

[1] See also *Ber.*, 1900, **33**, 668. [2] Willstätter, *Ann.*, 1901, **317**, 204. [3] Willstätter and Veraguth, *Ber.*, 1907, **40**, 957. Willstätter and Waser, *Ber.*, 1911, **44**, 3423. For cyclo-octadiene see also Döbner, *Ber.*, 1907, **40**, 146.

to yield dicyclo-octadiene. When the dihydrobromide of cyclo-octadiene is heated with alkalis or quinoline, hydrobromic acid is removed and another unsaturated hydrocarbon of the formula C_8H_{12} is produced. This boils at 143° to 144°, and perhaps corresponds to formula II. Whereas compound I is highly unstable and readily polymerises, the isomeric compound II is very stable. The latter is easily reduced to cyclo-octane by the Sabatier and Senderens method.

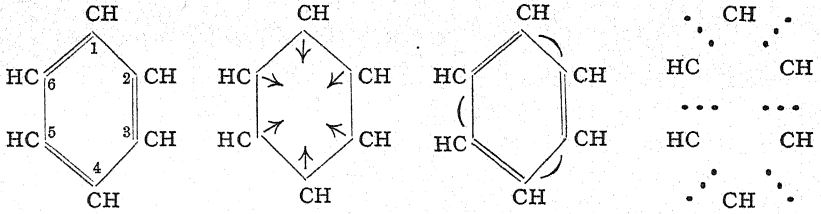
II

Introduction to the Aromatic Series

CONSTITUTION OF BENZENE

A very large number of compounds is derived from the hydrocarbon benzene, C_6H_6, many of which are of great importance industrially. Certain of these substances were obtained originally from aromatic oils and resins, and as they were of unknown constitution and possessed a pleasant odour, they were classed together as *aromatic compounds*. This term is now reserved for benzene derivatives.

The problem of the constitution of benzene was attacked many years ago by Kekulé and has not yet been finally solved. Three formulæ come into serious consideration, namely, that of Kekulé, the centric formula of Armstrong and Bamberger, and that proposed by Thiele.



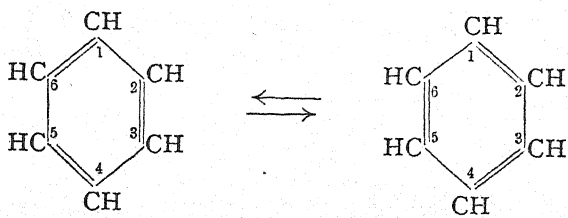
Kekulé | Armstrong and Bamberger | Thiele | Electronic formula.[1]

In proposing his formula for benzene, Kekulé [2] was guided by two regularities already established in connection with the chemistry of aromatic substances. Each benzene compound derived from the hydrocarbon by the replacement of one atom of hydrogen by another atom or radical existed in one form only. On the other hand, each di-substitution product of benzene occurred in three isomeric forms. From the first of these statements it followed that the six hydrogen atoms of benzene are chemically equivalent to one another, as was later shown conclusively by Ladenburg.[3] Accordingly, the benzene formula should have each of the six hydrogen atoms attached in a similar manner to carbon, a condition which is fulfilled by the formulæ $C_4(CH_3)_2$, $C_3(CH_2)_3$, and $(CH)_6$. Of these, however, only the last satisfies the second condition,

[1] For an alternative see p. 28. [2] Kekulé, *Ann.*, 1866, **137**, 129. [3] Ladenburg, *Ber.*, 1874, **7**, 1684.

that three isomeric di-substitution products should be possible. Hence Kekulé came to the conclusion that benzene must contain a closed chain of six carbon atoms, to each of which is attached one hydrogen atom. A doubtful point in this formula is the position of the fourth valency of the carbon atoms. Kekulé suggested that each carbon was linked to one of its two neighbours by a double bond, thus arriving at the above formula for benzene.

Kekulé's formula, however, does not satisfy all the requirements. It was first pointed out by Ladenburg that the existence of four structurally isomeric di-substitution products would be expected from a configuration of this kind, whereas, as already mentioned, the observed number is always three. In addition to the three di-derivatives represented by the positions 1 : 2, 1 : 3, and 1 : 4, there would be expected, according to the Kekulé formula, a fourth isomer of the type 1 : 6, since this differs from the 1 : 2 position in the arrangement of the double bond. By means of a further hypothesis Kekulé was able to bring his formula into harmony with the experimental facts. The single and double bonds were assumed to oscillate rapidly between the alternative positions as shown in the following formulæ :



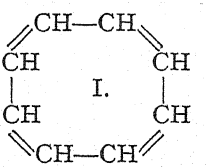
On this view any distinction between positions 1 : 2 and 1 : 6 disappears, and the occurrence of more than three di-substitution products is impossible. When it was first put forward Kekulé's oscillation theory assumed the existence of a property peculiar to the benzene ring. To-day, in the light of our present knowledge, it may be regarded as a special case of tautomerism.

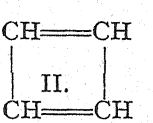
In so far as their mechanism is understood, all syntheses of benzene and its derivatives appear to support the Kekulé formula. As modified by the oscillation hypothesis, it would long ago have found general acceptance but for the fact that in its chemical character benzene is much less unsaturated than the olefins, and resembles rather the hydrocarbons of the saturated series. Halogens, for example, only unite with difficulty with benzene, whereas they combine instantaneously with aliphatic compounds containing multiple bonds. Benzene is also very stable towards oxidising agents and does not react at all with alkaline potassium permanganate, which is a specific reagent for ethylene derivatives.

The advocates of the centric formula of Armstrong and Bamberger (p. 359) claimed to be able to explain these anomalies. In this formula the fourth valencies of the carbon atoms, which cannot be utilised individually for ring formation or combination with other atoms, are supposed

to be directed towards the centre of the ring, where they neutralise one another. Since no such mode of linking is known in the aliphatic series, an explanation was thus provided for the existence of those " aromatic " properties peculiar to benzene derivatives. In common with many other formulæ which have been advanced from time to time, this also has points of weakness. It is difficult to see why the hypothesis of centrally directed bonds should be limited to the simple hexagon ring, but if it be applied to the polynuclear ring systems of naphthalene, anthracene and phenanthrene, the formulæ so deduced do not harmonise with the chemical properties of these compounds.

In a somewhat different manner Thiele attempted to explain the almost completely saturated properties of the benzene ring. Reference has already been made on p. 22 to his work on compounds containing conjugated double bonds, as a result of which he put forward the hypothesis that the affinities in the ordinary double bond were not completely utilised, but left residual or " partial valencies " in excess. Where two double bonds are in the conjugated position, the residual valencies on the two central atoms are supposed mutually to satisfy one another. This conception has also been extended to the benzene formula of Kekulé, which represents a closed system of conjugated double bonds, and leads to the conclusion that the residual affinities of the double bonds are completely saturated, as expressed in Thiele's formula on p. 359. Nevertheless, cyclo-octatetraene (I) is stated by Willstätter to be strongly unsaturated and very unstable.[1] Cyclo-butadiene (II) is apparently so unstable that it has not yet been isolated. Thiele's hypothesis cannot therefore be applied to all ring systems containing an alternation of single and double bonds.





An electronic formula based on the Kekulé structure has been reproduced on p. 28. This, however, is not in harmony with X-ray analyses of benzene, from which it is found that the distance between each pair of carbon atoms is 1·39 Å. It will be seen that this length is less than that of the single bond (1·54 Å) and somewhat more than that of the double bond (1·34 Å) in an aliphatic compound. An alternative electronic formula (see p. 359) due to J. J. Thomson assumes each pair of carbon atoms to be linked by three electrons. Such an arrangement is in agreement with most of the experimental facts but is difficult to bring into line with the wave mechanical interpretation of atomic linkages.[2]

[1] It appears doubtful if the compound examined by Willstätter was actually cyclo-octatetraene, see Goldwasser and Taylor, *J. A. C. S.*, 1939, **61**, 1260. [2] See Pauling, *J. A. C. S.*, 1931, 3228; *Nature*, 1932, **129**, 973; *ibid.*, **130**, 273.

At present *benzene is regarded as a resonance hybrid of the two Kekulé forms, i.e.* the actual electronic structure is supposed to be intermediate between these two extremes. This structure cannot be represented diagrammatically and the Kekulé formula [1] is therefore generally employed.

ISOMERISM IN THE BENZENE SERIES

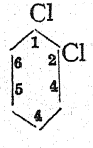
If one of the hydrogen atoms in benzene be replaced by another element or radical, the resulting *mono-substitution product exists in one form only*. There is thus only one monochloro-benzene, C_6H_5Cl, one monoamino-benzene, $C_6H_5NH_2$, and so on. Hence in this case the position assigned to the substituent group is immaterial, owing to the equivalence of the six hydrogen atoms.

If two hydrogen atoms of benzene are replaced by two monovalent elements or radicals,[2] the relative positions of the substituents greatly influence the properties of the compound.

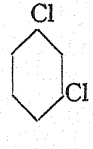
All di-substitution products exist in three isomeric forms. If we indicate the position of the first substituent with the figure 1, the three compounds formed by the introduction of a second substituent may be written as follows :

$$1:2 = 1:6, \quad 1:3 = 1:5, \quad \text{and} \quad 1:4$$

The derivative formed by substitution in position 2 or 6 is known as an *ortho*-compound, that in position 3 or 5 as a *meta*-compound, and that in position 4 as a *para*-compound. Usually these are contracted to *o*-, *m*-, and *p*-, or 1 : 2-, 1 : 3- and 1 : 4-, *e.g.*,



o- or 1 : 2-
Dichlorobenzene



m- or 1 : 3-
Dichlorobenzene

p- or 1 : 4-
Dichlorobenzene.

Even when the two substituents are different, three and only three isomerides are known.

The case is otherwise, however, when three hydrogen atoms are replaced by three monovalent elements or radicals. *If the substituents are the same, each trisubstitution product can occur in three isomeric* forms. These are distinguished from one another as vicinal (1 : 2 : 3)-, unsymmetrical (1 : 2 : 4)-, and symmetrical (1 : 3 : 5)-derivatives of benzene, and are usually written with the corresponding numbers or the abbreviation *v*-, *as*-,or *s*-, before the name of the compound, *e.g.*,

v- or 1 : 2 : 3-trichlorobenzene ; *as*- or 1 : 2 : 4-trichlorobenzene ;
s- or 1 : 3 : 5-trichlorobenzene.

[1] To simplify the formulæ and enable the relative positions of substituents to be clearly indicated, the benzene nucleus is commonly represented by a simple hexagon. [2] A polyvalent element never replaces several hydrogen atoms simultaneously in the same benzene nucleus. Compounds such as $C_6H_4{=}O$ or $C_6H_3{\equiv}N$ are unknown.

On the other hand, when the three substituents are not all the same the number of isomerides is greater than three. Should two be identical, as in the case of the compound $C_6H_3Cl(OH)_2$, six isomerides are possible; and if each of the three substituent groups is different, as in the compound $C_6H_3Cl(OH)CH_3$, theory predicts the existence of twelve isomerides.

With the entry of four similar substituents into the benzene nucleus, the number of isomerides is once again reduced to three, since the two remaining hydrogen atoms in the ring must occupy the ortho-, meta- or para-positions. If the four substituents are different the number of isomers is even greater than in the case of three unlike substituents.

Finally, if five hydrogen atoms are replaced by the same element or radical, as in C_6HCl_5, there is again only one compound possible.

Aliphatic radicals such as $-CH_3$, $-C_2H_5$, or $-CH:CH_2$ attached to the benzene molecule are known as *side chains*, and the rest of the molecule is termed the *nucleus* or benzene nucleus. Derivatives of this type possess the character of both aromatic and aliphatic compounds, and on further substitution may yield isomerides of quite different properties, depending on whether the substituent enters the nucleus or side chain, *e.g.*,

$C_6H_4Cl.CH_3$	$C_6H_5.CH_2Cl$
Chlorotoluene	Benzyl chloride.

Comparison of Aromatic and Aliphatic Derivatives

The properties of benzene derivatives which serve to differentiate aromatic from aliphatic compounds depend on the peculiar character of the benzene nucleus, and may be summarised as follows :—

1. A most striking feature is the ease with which hydrogen in an aromatic nucleus may be substituted by the nitro group ($-NO_2$), the sulphonic group ($-SO_3H$), or halogen. As mentioned on p. 107, the normal paraffins are attacked little or not at all by concentrated nitric or sulphuric acid,[1] whereas the aromatic hydrocarbons and almost all benzene derivatives are readily nitrated with concentrated nitric acid, or a mixture of the latter with concentrated sulphuric acid :—

$$C_6H_6+HO.NO_2 = \underset{\text{Nitrobenzene.}}{C_6H_5.NO_2}+H_2O$$

With concentrated sulphuric acid alone, aromatic compounds are readily converted into sulphonic acids :

$$C_6H_6+HO.SO_3H = \underset{\text{Benzene-sulphonic acid.}}{C_6H_5.SO_3H}+H_2O$$

2. Homologues of benzene, such as $C_6H_5.CH_3$ and $C_6H_5.CH_2.CH_2.CH_3$, differ from the paraffins in the ease with which they undergo oxidation; the latter resist attack, while the former are readily converted into benzene carboxylic acids such as $C_6H_5.COOH$, the whole of the side chain being oxidised away and replaced by a carboxyl group.

[1] Nitro-derivatives can only be obtained directly from aliphatic hydrocarbons by the action of *dilute* nitric acid at high temperatures.

3. A peculiar property of aromatic halogen compounds as compared with the alkyl halides is the relatively indifferent nature of the halogen atom. In chlorobenzene and bromobenzene, for example, the halogen is so firmly united to the nucleus that it can only be brought into reaction with alcoholates, ammonia and amines with the greatest of difficulty.

4. Aromatic amines are less basic than fatty amines, and the phenols, *e.g.* C_6H_5OH, are more strongly acidic than the alcohols.

5. Finally, it may be mentioned that, as in the aliphatic series, the reduction of aromatic nitro-compounds leads eventually to the formation of amines, but in this case intermediate reduction products known as azo-compounds and azoxy-compounds are first obtained. In addition, aromatic amines react with nitrous acid to give diazo-derivatives. These classes of compounds are only rarely found in the aliphatic series.

Directive Influence of Substituents in the Benzene Nucleus[1]

The nature of a substituent already present in the benzene ring exerts a decisive influence on the position taken up by a second entrant. In this connection a close relationship exists between the *ortho-* and *para-*positions which distinguishes them sharply from the *meta*-position. The hydroxyl group (OH), amino group (NH_2) and alkyl groups, for example, direct a newly entering element or radical preferably to the *o-* and *p-*positions, whereas a group such as NO_2 or SO_3H directs mainly to the *m*-position. In general, *o, p*-directive groups facilitate further substitution, whilst those of *m*-directive type increase its difficulty.

A systematic comparison of the directive powers of different groups was begun in 1895 by Holleman,[1] who measured the velocity of various reactions under standard conditions. Nitrations, for example, were conducted at 0° using fuming nitric acid. The relative directive powers of two groups were determined by introducing a third substituent into a benzene ring in which the two groups were already present, followed by a quantitative analysis of the resulting mixture. For the latter purpose, new methods of estimation had to be devised, one of the most useful being by means of fusion curves. Thus *p*-chlorotoluene on nitration gave a product containing more of the isomeride in which a nitro group is ortho to chlorine than of that having the nitro group ortho to methyl. Chlorine was therefore concluded to have a stronger directive power than methyl. One of the most interesting points which emerged from this work was that in the majority of cases where a monosubstituted benzene is further substituted, the reaction leads to a mixture of *o*,- *m*- and *p*-derivatives, although generally in very unequal proportions.

Holleman found that *m*-directing groups were more weakly directing

[1] Compare Holleman, *Die direkte Einführung von Substituenten in den Benzolkern* (Veit & Co., Leipzig, 1910). Reese, *Chem. Rev.*, 1934, 55.

than the *op*-directive groups, and expressed some of his conclusions as follows :

op-*Substitution, proceeds rapidly.*

$^{-}OH > NH_2 > NHAcyl > Cl > Br > CH_3 > alkyls > I$

m-*Substitution, proceeds slowly.*

$COOH > SO_3H > NO_2$.

Many attempts have been made to classify elements and radicals according to their directive influence, some of the more important of which may be mentioned briefly.

Among the earliest suggestions are those advanced independently by *Hübner*, *Nölting* and *Körner* about 1875, according to which basic or weakly acidic groups (NH_2, CH_3, OH, Cl) direct to the *o*- and *p*-positions, whereas strongly acidic groups (COOH, NO_2, SO_3H) lead to *m*-substitution.

The *Crum Brown and Gibson rule* [1] states that if the radical already present (CHO, COOH, NO_2, SO_3H) forms a compound with hydrogen which can readily be converted by direct oxidation into the corresponding hydroxyl compound, the second substituent will enter the meta-position. Otherwise it will assume the ortho- and para-positions.

Vorländer's rule divides substituents into unsaturated groups (NO_2, CN, COOH and SO_3H) causing *m*-substitution, and saturated substituents (Cl, Br, OH, CH_3) leading to *o*- and *p*-substitution.

Unfortunately, although these rules apply to the majority of the simpler cases, they are subject to exceptions and on occasion are mutually contradictory. Cinnamic acid, for example, with the acidic unsaturated substituent —CH=CH—COOH, nitrates in the ortho- and para-positions. Moreover, the normal directive influence of COOH or NH_2 may be largely reversed by ionisation. Sodium benzoate in an aqueous solution is chlorinated in the *o*- and *p*-positions ; and aniline in the presence of a large excess of sulphuric acid is nitrated mainly in the *m*-position.

Two other rules of orientation which have been advanced recently appear to be of general application. *Hammick* and *Illingworth* [2] have pointed out that in a compound C_6H_5XY, when Y is in a higher periodic group than X, or if being in the same group it is of lower atomic weight, then XY is *m*-directive. In other cases, including those in which the substituent is represented by a single atom (C_6H_5X), *op*-substitution follows.

Sutton has shown [3] that the directive influence of the substituent group X is related to the sign of the difference between the dipole moment of the aromatic compound Aryl X and that of the aliphatic analogue Alphyl X. If the expression ($\mu_{\text{Aryl X}} - \mu_{\text{Alphyl X}}$) is positive in value then X is *op*-directive ; if the expression is negative then X is *m*-directive. All values of μ are determined for benzene solutions, and where possible comparable data are employed by using those for aliphatic compounds

[1] *J. C. S.*, 1892, 61, 367. [2] *J. C. S.*, 1930, 2358. [3] *Proc. Roy. Soc.*, 1931, **133 A**, 668.

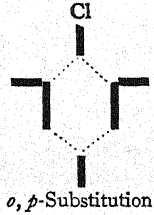
in which X is linked to a tertiary carbon atom. Some of these values are given in the following table.

X.	μ Aryl X.	μ Alphyl X.	Diff.	Directive Effect.
CH_3	+0·41	0	+0·41	*op*
Cl	−1·56	−2·15	+0·59	*op*
Br	−1·53	−2·21	+0·68	*op*
I	−1·30	−2·13	+0·83	*op*
CH_2Cl	−1·82	−2·14	+0·32	*op*
CCl_3	−2·07	−1·57	−0·50	*m*
CN	−3·90	−3·46	−0·44	*m*
NO_2	−3·97	−3·29	−0·68	*m*

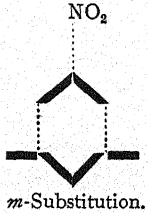
Additional confirmation of Sutton's work is provided by the data of Groves and Sugden relating to measurements in the vapour state.[1]

The differences are mainly due to the high polarisability of the benzene nucleus. They show that where the group X is *op*-directive there is an electron displacement from the substituent towards the ring; this permanent effect is therefore in the direction which facilitates *op*-substitution. With *m*-directive groups the displacement is in the opposite sense and assists *m*-substitution (compare electronic theory of benzene substitution).

Flürscheim's Theory of Substitution.—Flürscheim [2] has advanced a theory of benzene substitution based on Werner's hypothesis of maximum disposable affinity. When at any bond in a chain hydrogen is replaced by a substituent which differs from it in the amount of its "affinity demand," there results an alternating increase and decrease in the affinity content of successive bonds in the chain and a corresponding alternating increase and decrease of residual affinity at successive atoms. All those atoms which are capable of combining with varying equivalents of other atoms are in their lower state of combination endowed with considerable residual affinity (*e.g.* N in NH_2, monovalent halogens, and O in OH). When they replace hydrogen linked to carbon their affinity demand therefore exceeds that of hydrogen. The contrary state of affairs holds when atoms enter a bond in their highest state of combination (*e.g.* N in NO_2, S in SO_3H), in which case their affinity demand is less than that of hydrogen. According to the nature of the substituent present, the resulting alternation in a monosubstituted benzene is thus supposed to lead to an increase of free affinity at the *o*- and *p*-carbon atoms (*o*, *p*-substitution) or at the *m*-carbon atom (*m*-substitution).



o, *p*-Substitution



m-Substitution.

[1] *J. C. S.*, 1935, 973. [2] *J. pr. Ch.*, 1902, **66**, 321; *Ber.*, 1906, **39**, 2015; *J. S. C. I.* (*Chem. and Ind.*), 1925, **44**, 246.

Addition Hypothesis of Holleman.[1]—In the Kekulé formula for benzene a substituent X is always attached to a doubly bound carbon atom, and in such a structure it is known to have a low reactivity (see p. 135).

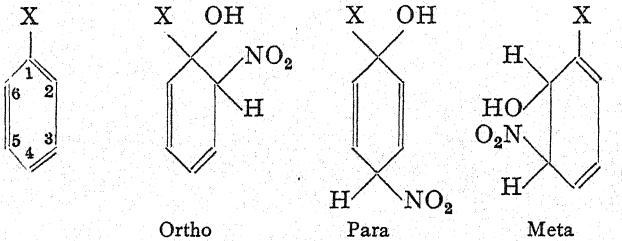
$CH_2:CCl.CH_3$ — Non-reactive halogen

$CH_2:CH.CH_2Cl$ — Reactive halogen.

Since the presence of the double bond thus influences the activity of X, Holleman suggests that the converse also holds true, and that the nature of X affects the character of the double bond.

According to Holleman the essential factor controlling the course of benzene substitution is the influence of X in facilitating or inhibiting addition to the adjacent double bond; and as this bond is part of a conjugated system the influence will also be propagated to the 1 : 4-position. The 5 : 6-bond is assumed to be comparatively unaffected.

Nitration is supposed to occur as a result of the two processes: 1. Addition of reagent, which may proceed in three ways, followed by 2. rapid elimination of water.



Ortho Para Meta

The type of reaction product will depend on the relative velocities of formation of the three addition compounds shown. If X makes the adjoining double bonds more reactive than a normal (5 : 6) bond, addition takes place leading to *o*- and *p*-substitution. If on the other hand activity is diminished, addition occurs at the 5 : 6-position and *m*-substitution ensues. A similar explanation is applied to the substitution by halogens, hydrogen halide being eliminated.

Some support for Holleman's theory is to be found in the occasional isolation of an addition compound during the nitration of olefin derivatives, *e.g.*[2]

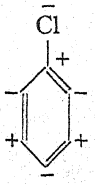
$$(C_6H_5)_2C{=}CH_2 \longrightarrow (C_6H_5)_2\overset{OH}{\underset{|}{C}}\!\!-\!\!\overset{NO_2}{\underset{|}{C}}H_2 \longrightarrow (C_6H_5)_2C{=}CHNO_2{+}H_2O$$

and during aromatic substitutions.[3] But the present view is that the majority of substitutions of aromatic compounds occur by direct attack of the reagent at a CH-group, and involve simultaneous addition of the entering group and removal of hydrogen.[4]

[1] *Rec. trav. Chim.*, 1895, **14**, 123. *Chem. Reviews*, 1924, **1**, 187. [2] Wieland and co-workers, *Ber.*, 1920, **53**, 201; 1921, **54**, 1770. [3] Barnett and Cook, *J. C. S.*, 1924, **125**, 1084. Fries and Engel, *Ann.*, 1924, **439**, 232. [4] *Cf.* London, *Z. Elektrochem.*, 1929, **35**, 552.

Electronic Theories of Benzene Substitution

The systematic work of Holleman on the directive powers of groups in benzene substitution was followed by many other investigations on practical and theoretical aspects of this problem. Among the more important theories may be mentioned Flürscheim's postulation of alternating strong and weak valency bonds which has already been described on p. 366. In *Lapworth's "key atom" hypothesis*,[1] the presence of an atom of strong polarity was assumed to set up an alternation of positive and negative polarities in the chain to which it was linked, an alternation which could only be effectively propagated along a system of conjugated double bonds. Thus the electronegative atom chlorine was regarded as giving rise to the alternate polarities shown in the diagram, directing an attacking positive group ($\overset{+}{N}O_2$ or $\overset{+}{B}r$) to the *o*- and *p*-positions. Nitrogen in the nitro group was represented as a positive key atom ($.\overset{+-}{N}O_2$), leading to the opposite type of alternation and so to *m*-substitution. Fry advanced an electronic theory[2] which assumed the occurrence of positive and negative charges on alternate carbon atoms. All these theories have contributed to the present point of view as represented in the electronic theories elaborated by Robinson[3] and Ingold.[4] In giving a brief outline of this latest development, a resumé may also be made of the main experimental facts on which it is based and of the typically aromatic reactions it attempts to explain.



The most striking characteristics of aromatic chemistry are the predominantly *op*- or *m*-directive influence of groups attached to the nucleus and the rapidity of the former type of substitution as compared with the latter, a peculiarity which was first emphasised by Holleman. Additional information on this point has been provided by Wibaut[5] and Ingold,[6] who showed that toluene is nitrated fourteen times as fast as benzene, thus proving that even the methyl group strongly facilitates substitution in the ring. On the other hand, halogenated benzenes are exceptional in being attacked more slowly than benzene itself, although they also yield *o*- and *p*-derivatives.

The most powerful directive influence of all is exerted by a substituent bearing an integral charge such as the ionised hydroxyl group ($\overline{O}$) of phenoxides,[7] which are brominated with great velocity and almost entirely in the *o*- and *p*-positions, and the $\overset{+}{N}Me_3$ group of phenyltrimethylammonium salts which slowly yield a pure *m*-derivative. The remarkable influence of this last group is illustrated in the following percentages of

[1] *Mem. Manchester Phil. Soc.*, 1920, **64**, No. 3; *J. C. S.*, 1922, **121**, 416. [2] *The Electronic Conception of Valence* (Longmans, 1921). [3] Robinson, "Outline of an Electrochemical Theory of the Course of Organic Reactions" (Institute of Chemistry, 1932). [4] Ingold, *Chem. Rev.*, 1934, **15**, 225; *Rec. trav. Chim.*, 1929, **48**, 805. [5] Wibaut, *Rec. trav. Chim.*, 1915, **34**, 241. [6] Ingold and Shaw, *J. C. S.*, 1927, 2918. [7] See Soper and Smith, *J. C. S.*, 1926, 1582; 1927, 2757.

m-compound formed,[1] corresponding data for the strongly *m*-directive nitro group being also given.

$C_6H_5.\overset{+}{N}Me_3$	$C_6H_5.CH_2.\overset{+}{N}Me_3$	$C_6H_5.CH_2.CH_2.\overset{+}{N}Me_3$
100	88	19
$C_6H_5.NO_2$	$C_6H_5.CH_2.NO_2$	$C_6H_5.CH_2.CH_2.NO_2$
93	48	13

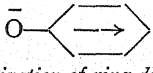
Even when separated from the nucleus by two carbon atoms, the trimethylammonium group gives rise to no less than 19 per cent. of *m*-derivative.

Comparisons of the above nature inevitably led to the conclusion that *the aromatic nucleus is activated by negatively charged substituents and deactivated by those carrying a positive charge.* They also confirmed the belief that the attacking reagent is *electrophilic* [2] in character, seeking a point in the molecule at which there is a high electron density. In bromination, for example, one bromine atom appears in the final mixture as bromide ion; the effective agent is thus positively charged bromine liberated by the unsymmetrical disruption of molecular bromine.

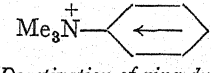
$$Br\vdots Br \longrightarrow Br^+ + Br^-$$

Similarly, nitric acid reacts in the form $HO.NO_2$, the hydroxyl taking with it on separation both of the covalency electrons originally binding it to nitrogen and leaving the positive residue $^+NO_2$ to attach itself to the nucleus at a point where the nitrogen octet may be completed.

According to the electronic theories of Robinson and Ingold, one way in which the influence of a negatively or positively charged substituent is passed on to the ring is by **inductive effect** (see p. 83). A negatively charged group will repel the covalency electrons in the nucleus and so render them more readily available to a suitable reagent; a positively charged group will attract the electrons and thus reduce the reactivity of the ring. These conditions are represented diagrammatically as follows.

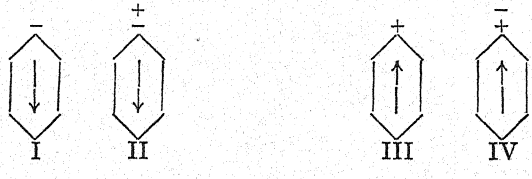


Activation of ring due to increased electron-availability.



Deactivation of ring due to lowered electron-availability.

Less powerful influences of the same kind are assumed to arise from the dipoles of polar groups, whether electropositive (CH_3, NH_2) as in II, or electronegative (NO_2, COOH, SO_3H) as in IV. In these cases the



I II III IV

[1] Ingold, *Rec. trav. Chim.*, 1929, **48**, 805. For similar effects in oxonium and quinolinium salts see R. J. W. Le Fèvre and co-workers, *J. C. S.*, 1929, 2771; 1930, 2236. [2] This type is often described as kationoid.

effect is caused by one pole of the dipole being nearer the ring than the other, and the inductive influences are naturally weaker than those due to an ionic group. Ingold describes the change in the nucleus [1] indicated in I and II as a +I effect, and the reverse change shown in III and IV as −I.

The characteristic properties of aromatic compounds, however, cannot be adequately interpreted in terms of the inductive effect alone. No explanation is provided for the alternation of reactive and non-reactive points in the aromatic ring, nor for the fact that the speed of substitution by electrophilic agents is not reduced by *all* electronegative groups. Some substituents, notably hydroxy and alkoxyl, resemble the electropositive methyl, amino and alkylamino groups in leading to a greatly increased rate of attack.

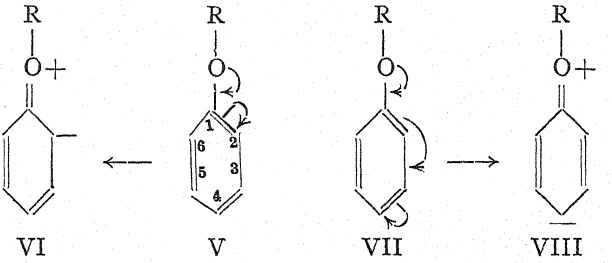
A similar difficulty arises in tracing the effect of a substituent on acidic strength. Nathan and Watson [2] have shown that the dipole moment of a group X present in an aliphatic acid, $X.CH_2.COOH$, may be directly correlated with the dissociation constant of the acid. But this simple relationship does not hold for aromatic acids. A methoxyl group increases the dissociation constant of acetic acid and also of benzoic acid when present in the *m*-position, whereas the same group in the *p*-position considerably lowers the strength of benzoic acid. On the other hand, a nitro group in the *p*-position raises the dissociation constant of benzoic acid more than one in the *m*-position, despite its greater proximity to the carboxyl group in the latter case. Halogens exert a greater influence in the *m*- than in the *p*-position, but their relative effects among themselves are not the same as those found in the acetic acid series.

It thus became clear that an electrical effect of another type is being relayed from the substituent group, and one which may on occasion act in opposition to the induced effect. This second factor, known as the **tautomeric effect,** is based on Lowry's idea of *electromeric change* (see p. 89) and the modern conception of mesomerism. A clue to its nature was given by the observation that abnormal results follow the introduction of groups having unshared electrons on the atom linked to the nucleus. Such an atom has the possibility of transferring a pair of electrons by electromeric change so as to form a double bond between it and the adjoining carbon atom. By further electromeric rearrangement an ortho- or para-quinonoid structure may be formed. This transformation is readily visualised in the case of hydroxy and amino derivatives, since quinones and quinonimines represent well-known structures.

In an alkoxy benzene the process may be formulated provisionally in the following way. On the completion of the double bond between O and C_1 (see fig. V), the valency sheath of the latter is reduced to eight

[1] Robinson suggests that these signs should be reversed so as to represent the charge conferred by the group on adjacent atoms, a nomenclature which has been adopted in American publications. Ingold's system is at present more generally used in British journals and has the advantage that the signs are the same as those of the controlling dipoles. [2] *J. C. S.*, 1933, 893.

again by the release of two electrons from the double bond C_1C_2, converting this into a single bond.



VI V VII VIII

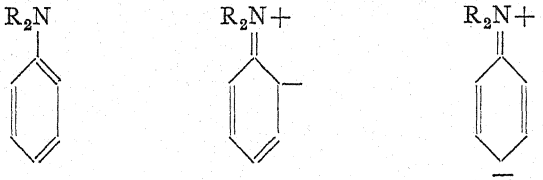
The released electrons may then remain in the unshared state on C_2, yielding the *o*-quinonoid form VI, which will undergo substitution most readily in the negatively charged *o*-position. Alternatively, the charge may be passed on directly from C_1C_2 to C_2C_3 (see fig. VII), transforming the single into a double bond, followed by the withdrawal of two electrons of the C_3C_4 double bond to C_4, in order to bring the number at the *m*-position down to eight. The negative charge in the resulting *p*-quinonoid structure VIII is at C_4, leading to substitution at this point. Without violation of the octet rule the charge cannot be represented as remaining at the *m*-position, hence activation occurs at the *o*- and *p*-positions.

The theory, however, regards the alkoxy benzene as existing in a definite state of mesomerism, with each of the forms V, VI and VIII, as well as the corresponding arrangements derived from the other Kekulé form having double bonds at 2 : 3, 4 : 5 and 1 : 6, making its contribution to the actual resonance structure. The latter is therefore more correctly formulated with small negative charges ($\delta-$) at the *o*- and *p*-positions, which arise as indicated from the *incomplete* electron displacements. The assumption of a permanent polarisation of this kind is supported by Sutton's generalisation on dipole moments of aliphatic and aromatic compounds of the type RX already discussed on p. 365. Ingold describes it as the **mesomeric effect,** M, prefixed in the case under consideration by a positive sign (+M). At the demand of a suitable reagent, situated in proximity to an activated position, reaction ensues leading to the *completed* electromeric change (+E) shown in the above mechanism. The tautomeric effect is therefore made up of the two effects respectively described as mesomeric and electromeric, T = M+E.

The final stages of reaction may be illustrated in the case of bromination. After Br^+ has attached itself to the negatively charged carbon atom ($>\bar{C}H$) to form the neutral group $>CHBr$, the proton is assumed to become detached, leaving carbon once again with a negative charge as $>\bar{C}Br$. By a reversal of the electromeric changes already depicted, the positive and negative charges are neutralised, leaving the ring in the normal aromatic state ($\geqslant CBr$).

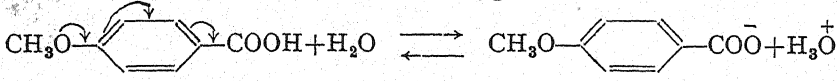
Amino-compounds and their alkyl derivatives may give rise to a

tautomeric effect similar to that of hydroxy and alkoxy compounds, leading to contributing structures of the types IX, X and XI.



IX X XI

Electromeric displacements of this kind also serve to explain some of the abnormalities observed in the dissociation constants of aromatic acids. Reference has already been made to the fact that whilst a methoxyl group increases the acid strength of acetic acid, it lowers that of benzoic acid when present in the *p*-position. Increased covalency between oxygen and the nuclear carbon atom in the *p*-compound results in a greater electron-availability at the carboxylic oxygen atoms, and thus tends to

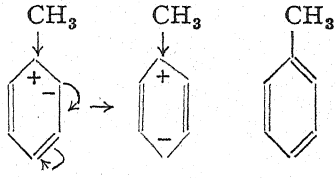


bind more firmly the ionisable hydrogen. For reasons just indicated these displacements cannot be relayed from the *m*-position, and a methoxyl group at this point exerts its normal inductive influence, producing a slight increase in the dissociation constant as compared with benzoic acid. Similar effects have been noted in side chain reactions of " type A " described on p. 85.

Among the remaining types of *op*-directive substituents, halogens and alkyl groups have also been investigated, but here the mechanism by which the influence is transmitted is not so clearly established.[1] It is probable that with halogens the same inductive and tautomeric effects operate as have been postulated in the case of alkoxy compounds, even though the corresponding quinonoid forms resulting from increased covalence of halogen with the ring have not actually been isolated. With alkyl benzenes there is no possibility of a tautomeric effect, since there are no unshared electrons on the carbon atom of the alkyl group attached to the nucleus. A methyl group, however, exerts a definite if small electron-repulsion, as shown by its influence in weakly depressing the acidic strength of an aliphatic acid and by the small positive dipole moment of toluene. The directive power of the group is therefore believed to be due to an inductive effect, which leads primarily to the polarisation of the adjacent double bond, C_1C_2, so that on activation the negative pole is developed in the ortho position (XII). By electromeric change the structure XII may be transformed into XIII. These two types may thus be regarded, together with XIV, as contributing to the mesomeric state. The general inductive effect (+I) means that there will be an

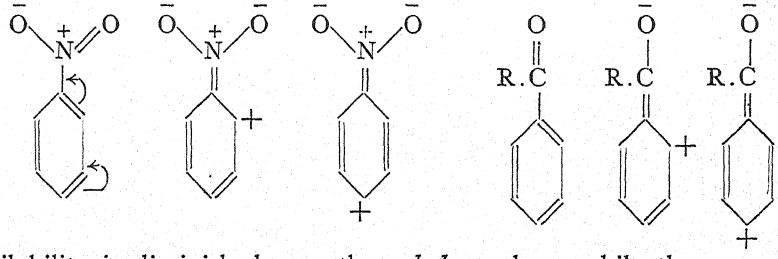
[1] For a discussion of these cases see Ingold, *Chem. Rev.*, 1934, **15**, 238 ; H. B. Watson, *Modern Theories of Organic Chemistry* (Oxford, 1937), pp. 70-80.

increased electron-availability at *all* points in the ring. This has been proved by nitration of toluene with acetyl nitrate, when, in comparison with benzene as standard, the *o*-, *m*- and *p*-positions are attacked at the rates of 40, 3 and 51 respectively.[1] Support for the above interpretation is found in the dissociation constants of the toluic acids, the value for the *p*-compound being somewhat less than that for the *m*-derivative.[2]



XII XIII XIV

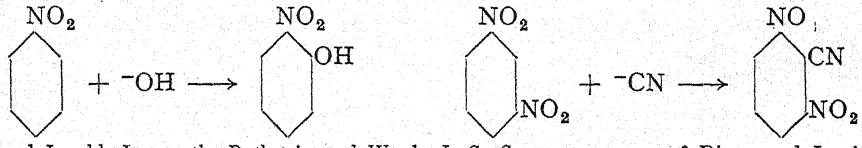
m-Directive groups also have no unshared electrons on the atom linked to the ring. All such substituents are strongly electronegative and are represented as giving rise to electromeric displacements in the opposite direction to those developed in alkyl or alkoxy derivatives. A typical case is that of a nitro-compound, for which the forms contributing to the resonance structure are shown below. In the normal state, therefore, the compound may be regarded as having fractional positive charges at the *o*- and *p*-positions. Owing to the inductive effect (—I), the electron-



availability is diminished over the *whole* nucleus, while the mesomeric effect (—M) results in deactivation being particularly evident in the *o*- and *p*-positions. Hence substitution proceeds comparatively slowly and at the *m*-position.

A similar state of affairs occurs when the directive substituent is a ketonic group. In all cases the structures derived from the Kekulé form with the double bonds in the alternate positions also contribute to the resonance state.

On the foregoing theory of benzene substitution it is to be expected that the normal directive powers of groups will be reversed when the reagent is **nucleophilic** instead of electrophilic in character, *i.e.* one containing an atom with its full complement of electrons and able to play the part of a "donor" towards an "acceptor" with an incomplete sheath. Reactions of this kind are already well known. Thus nitrobenzene heated with strong potassium hydroxide yields *o*-nitrophenol,[3]



[1] Ingold, Lapworth, Rothstein and Ward, *J. C. S.*, 1931, 1959. [2] Dippy and Lewis, *J. C. S.*, 1936, 644. [3] Wohl, *Ber.*, 1899, **32**, 3486.

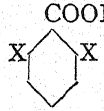
and *m*-dinitrobenzene reacts with potassium cyanide to give 2 : 6-dinitrobenzonitrile.[1] The nuclear hydrogen is eliminated during these changes in the form of potassium hydride. Another example of the same kind is the interaction of pyridine with sodamide ($^-NH_2$) to produce 2-aminopyridine,[2] in which connection it may be noted that electrophilic reagents attack pyridine in position 3.

Reactivity of Benzene Derivatives

Although halogen attached directly to the benzene nucleus does not readily enter into reaction, it may do so under the influence of other substituents present in the ring. For example, the occurrence of a nitro group in the ortho- or para-position to a halogen atom increases the reactivity of the latter, rendering it more readily exchanged for other groups or atoms. The same substituent in the meta-position, on the other hand, does not induce this change. Similarly, bromine in *o*-bromobenzoic acid is very reactive in the presence of copper acetate or copper powder. When an aqueous solution of the acid is boiled for a short time with a mixture of sodium acetate and copper acetate it is converted into salicylic acid. With sodio-malonic ester in the presence of copper powder, the acid yields *o*-carboxyphenyl malonic ester.[3] Under these conditions the chloro-acid is non-reactive.

Phenoxy and alkoxy groups have the property of increasing the reactivity of an α-bromine atom contained in a hydrocarbon radical in the ortho- or para-position to them, *e.g.* *o*-$CH_3O.C_6H_4.CH_2Br$.[4]

Ortho-substituents occasionally exert a surprising influence in hindering or even completely preventing the progress of such reactions as would otherwise proceed with ease. Numerous examples of *steric hindrance* of this type will be met with in the following pages, the best known instances being those discovered by Victor Meyer in connection with the *esterification of aromatic acids*. It is found that whenever the two hydrogen atoms in the ortho-positions to the carboxyl group of benzoic acid are replaced by atoms or radicals such as Cl, Br, NO_2, CH_3, or COOH, the resulting acid (see annexed formula) cannot be esterified with alcohol and hydrochloric acid, or only with extreme difficulty. Similarly, if an acid of this type is once converted into its ester by other means (*e.g.* by use of the silver salt and ethyl iodide), the ester is very difficult to hydrolyse.



Formation of Cyclic from Open-chain Compounds

Aliphatic compounds may be transformed into those of the aromatic series in a number of ways, one of which is of historical interest and has

[1] Lobry de Bruyn, *Rec. trav. Chim.*, 1889, **2**, 210. [2] Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216. [3] W. R. H. Hurtley, *J. C. S.*, **1929**, 1870. [4] A. Werner, *Ber.*, 1906, **39**, 27; for a suggested explanation see A. Lapworth and J. B. Shoesmith, *J. C. S.*, 1922, **121**, 1391.

already been referred to on p. 261. A few of the more important methods are given below.

1. When submitted to a high temperature many methane derivatives yield benzene compounds among other products (see cracking processes, p. 114).

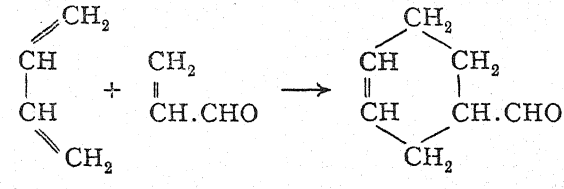
2. In the same manner acetylene polymerises to benzene, $3C_2H_2 = C_6H_6$, and other aromatic hydrocarbons [1]; monobromo acetylene gives 1 : 3 : 5-tribromo-benzene, $3C_2HBr = C_6H_3Br_3$; treatment with concentrated sulphuric acid converts allylene into mesitylene or 1 : 3 : 5-trimethyl-benzene, $3CH : C.CH_3 = C_6H_3(CH_3)_3$.

3. Acetone also yields mesitylene when treated with sulphuric acid, $3CH_3.CO.CH_3 = C_6H_3(CH_3)_3 + 3H_2O$. In a similar manner methyl-ethyl-ketone, $CH_3.CO.C_2H_5$, gives 1 : 3 : 5-triethyl-benzene, $C_6H_3(C_2H_5)_3$; and formylacetone, $CH_3.CO.CH_2.CHO$, passes rapidly into 1 : 3 : 5-triacetyl-benzene, $C_6H_3(CO.CH_3)_3$.

4. Potassium combines directly with carbon monoxide to form the potassium salt of hexahydroxy-benzene.

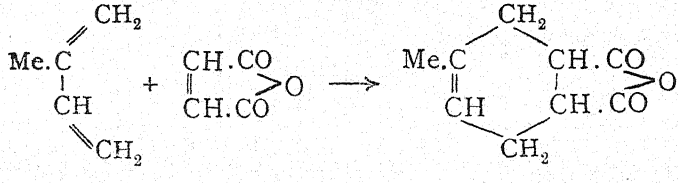
5. A valuable reaction of unsaturated compounds has been investigated by Diels and Alder. Butadiene and many of its derivatives have been found to react quantitatively with substances containing the group .CH : CH.CO., such as maleic anhydride, acrylic aldehyde, acrylic ester.[2] In many cases the interaction proceeds at room temperature. Combination occurs by the reactive group CH : CH.CO adding terminally to the butadiene, as in the following typical examples, resulting in the production of partially hydrogenated aromatic compounds.

I.



Butadiene — Acrylic aldehyde — Tetrahydro-benzaldehyde.

II.



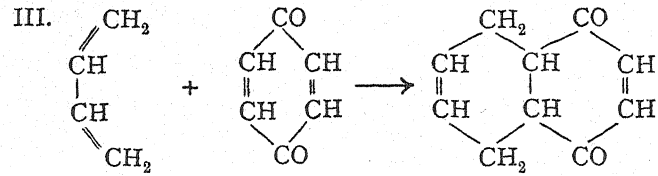
Isoprene — Maleic anhydride — Methyl-tetrahydro-phthalic anhydride.

This reaction is capable of very wide extension; for example, the

[1] R. Meyer and A. Tanzen, *Ber.*, 1913, **46**, 3183.

[2] O. Diels, K. Alder and co-workers *Ann.*, 1928, **460**, 98; *Ber.*, 1936, A, 195.

place of the above aliphatic keto-compounds may be taken by *p*-benzoquinone and α-naphthaquinone,

III. 

and that of butadiene by a variety of cyclic unsaturated hydrocarbons.

On the other hand, certain benzene derivatives, particularly phenols, aminophenols, quinones, hydroxy-quinones and phenol-carboxylic acids, may be converted into open-chain compounds. Thus benzene triozonide decomposes with water to give glyoxal; mesotartaric acid (see p. 284) has been obtained by the oxidation of phenol, C_6H_5OH, with dilute permanganate solution; and chloroquinone and finally maleic acid are formed when benzene is treated with potassium chlorate and sulphuric acid.

III

Benzene and its Homologues

Benzene is formed during the dry distillation of coal, and, as described in detail below, is prepared industrially from coal tar. It was first isolated by Faraday in 1825 from the illuminating gas obtained from oil; it was prepared from benzoic acid by Mitscherlich in 1834, and its presence in coal tar discovered in 1845 by A. W. Hofmann.

Benzene is a colourless, strongly refracting liquid of peculiar aromatic taste and smell, boiling at 80·4° under 760 mm. and melting at +5·4°. Sp. gr. 0·899 at 0°. It burns with a luminous sooty flame, is insoluble in water, but is miscible in all proportions with alcohol and ether, and forms an excellent solvent for resins, fats and sulphur. With an ammoniacal solution of nickelous cyanide it yields a white, violet-tinted crystalline compound of the formula NiC_2N_2, NH_3, C_6H_6, which may be used for the detection of benzene [1]; and with antimony pentachloride, according to the amount of solvent present, a yellow to yellow-red colour is developed.[2] When treated with chlorine, benzene forms both addition and substitution products, such as $C_6H_6Cl_2$, $C_6H_6Cl_4$, $C_6H_6Cl_6$ and C_6H_5Cl, $C_6H_4Cl_2$.

Concentrated sulphuric acid converts it into benzene sulphonic acid, nitric acid into nitrobenzene, and hydriodic acid into hexahydrobenzene. With ozone, benzene yields a triozonide, $C_6H_6(O_3)_3$, which is decomposed by water [3] to form glyoxal.

$$C_6H_6(O_3)_3 \longrightarrow 3O{:}CH.CH{:}O$$

[1] K. A. Hofmann and Arnoldi, *Ber.*, 1906, **39**, 339. [2] S. Hilpert and Wolf, *Ber.*, 1913, **46**, 2215. [3] Harries, *Ann.*, 1905, **343**, 335.

These and other chemical changes of benzene are discussed in detail in later chapters.

DRY DISTILLATION OF COAL AND MANUFACTURE OF COAL GAS

The main source of benzene and its methyl homologues is the tar obtained as a by-product when coal is submitted to dry distillation at temperatures above 1000° C., either for the manufacture of coal gas or of coke for metallurgical purposes. In the former process gas coals are employed, rich in hydrogen and yielding a high proportion of gas, whereas in coke ovens a coal poorer in hydrogen is utilised, which will give a good yield of a dense coke. Gas coke of open texture is, in addition, produced in relatively small amount in the manufacture of coal gas, and gas is also obtained from the coke ovens. Coal tar and an aqueous liquor containing ammonia (gas liquor) are obtained as by-products in both processes.

The distillation of gas coal is carried out in retorts of fireproof clay. Volatile products of decomposition are led through pipes to a trough, in which the bulk of the tar condenses. Coal gas passes on, and is freed from further quantities of tar and ammoniacal gas liquor by passage through specially constructed chambers which are well cooled with water. The remainder of the ammonia is removed by washing the gas in water. The gas is next freed from hydrogen cyanide, usually by washing with a solution of an iron salt, the resulting cyanogen compounds of iron being subsequently worked up for potassium ferrocyanide and other products. Finally, sulphur is removed, generally by leading the gas through cast-iron chambers containing hydrated ferric oxide spread out in thin layers.

The purified coal gas is collected over water in gas-holders or gasometers, and delivered under pressure into distributing pipes. It contains hydrogen (about 50 per cent. by volume), methane (35 per cent.) and carbon monoxide (8 per cent.) as non-luminous constituents, and ethylene, acetylene, benzene and naphthalene (totalling about 4 per cent.) as luminous constituents, together with carbon dioxide (1 per cent.), nitrogen (4 per cent.), hydrogen sulphide and ammonia as impurities.

From 100 kilos of coal are obtained on the average 27 to 30 cubic metres of gas, 5 kilos tar, 64 kilos coke and 100 kilos of ammoniacal gas liquor.

Up to the present time the distillation of coal by the above process has usually been so conducted that the primary products of distillation are—by contact with the red-hot walls of the retort—largely converted into compounds of an aromatic nature, which collect in the tar. According to recent investigations the **low temperature distillation of coal** may be effected at 600° under reduced pressure, to give a large primary *distillate of aliphatic character*. In this manner the typical products of the petroleum industry may be prepared from coal (see pp. 107 and 115).

The yield of tar from the low temperature process varies, according

to the starting material, from 8 to 12 parts as against the 4 to 5 parts obtained from the ordinary process in the manufacture of coal gas. The low temperature tar may be prepared either as the chief product of distillation in apparatus designed to this end, or as a by-product from the gas generator.

Coal Tar

Properties, Composition and Uses.—Coal tar as obtained from the manufacture of coal gas or the coke ovens is a black, viscous liquid of peculiar acrid smell. It is an extremely complex mixture of substances, which may be roughly divided into those of acidic, basic and neutral character. Among neutral products the most important are the hydrocarbons of the aromatic series—benzene and its homologues, naphthalene and anthracene—to which the industrial value of coal tar is mainly due. The content of naphthalene amounts to 5 to 10 per cent. of the tar, and of benzene and toluene to about 1 to 1·5 per cent. Basic constituents include compounds of the pyridine and quinoline group, while those of acidic nature are chiefly phenols, among which phenol itself predominates.

Coal tar is probably put to a greater variety of uses than any other substance. In the crude state, without any previous rectification, it is used for protecting the surface of masonry and wood, for impregnating wood, in the preparation of composition roofing, in the manufacture of lampblack and briquettes, and as fuel. Its chief value, however, lies in the products which can be obtained from it.

Distillation of Coal Tar.—Distillation is carried out in roomy stills which are bricked in, and the distillate is condensed in an iron coil condenser. Four fractions are usually collected as follows :—

1. *Light oil*, which is lighter than water and distils between 80° and 170°.
2. *Middle or carbolic oil*, sp. gr. approximately 1, which distils between 170° and 240°.
3. *Heavy or creosote oil*, which is heavier than water and distils between 240° and 270°.
4. *Green or anthracene oil*, which is green in colour and distils between 270° and 400°.

The *pitch* which is left as a residue in the retort is utilised in the preparation of varnish and lacquer, briquettes and other products.

For the production of benzene hydrocarbons the only fraction of importance is the light oil. This is washed with aqueous sodium hydroxide to remove acids, and with concentrated sulphuric acid to remove bases, and is then fractionated in a rectifying column. Benzene, toluene, $C_6H_5.CH_3$, and xylenes or dimethyl-benzenes, $C_6H_4(CH_3)_2$, are thus obtained in a relatively pure form, and are placed directly on the market. Methyl derivatives such as the three isomeric xylenes, and the trimethylbenzenes or cumenes, are rarely isolated in the pure state from light oil, but are usually employed in the crude condition as solvents for resins, fats, and so on. Like the other alkyl derivatives of benzene, they are also prepared synthetically.

Preparation of Benzene Homologues

Alkyl derivatives of benzene may be prepared by the condensation of alkyl-acetylenes (see p. 375) and by the following methods :—

1. By the dry distillation of aromatic carboxylic acids with alkali. In the same manner benzene may be obtained from benzoic acid.

$$C_6H_5.CO_2Na+NaOH = C_6H_6+Na_2CO_3$$

2. By the action of sodium on a mixture of a brominated benzene hydrocarbon and an alkyl bromide or iodide, *e.g.*,

$$C_6H_5Br+2Na+C_2H_5Br = \underset{\text{Ethyl-benzene}}{C_6H_5.C_2H_5}+2NaBr$$

This reaction, discovered by Fittig, is an extension of the Würtz method of synthesising paraffins by the use of sodium and alkyl halides (p. 111).

3. From aromatic organo-magnesium derivatives by heating with alkyl halides, or more conveniently by the action of alkyl sulphates.[1]

$$\underset{\text{Phenyl magnesium bromide}}{C_6H_5.MgBr} + \underset{\text{Dimethyl sulphate}}{(CH_3)_2SO_4} = \underset{\text{Methyl-benzene or toluene.}}{C_6H_5.CH_3} + Br.Mg.SO_4CH_3$$

In this connection it may be noted that alkylene benzene derivatives (1[1]-alkylated styroles), which are readily synthesised from alkyl magnesium halides (see p. 383), are easily reduced to the corresponding benzene hydrocarbons, thus providing a valuable means of preparing a series of otherwise difficultly accessible compounds. In this manner propenyl-benzene, $C_6H_5.CH:CH.CH_3$, yields *n*-propyl-benzene, $C_6H_5.CH_2.CH_2.CH_3$; and methovinyl-benzene, $C_6H_5.C(CH_3):CH_2$, yields isopropyl-benzene, $C_6H_5.CH(CH_3).CH_3$.

4. The *Friedel-Crafts reaction* is an important method of preparing alkyl-benzenes and aromatic ketones. It consists in bringing aromatic hydrocarbons into reaction with alkyl halides or acid chlorides (see p. 444), in the presence of anhydrous aluminium chloride.[2]

$$C_6H_6+Br.C_2H_5 = \underset{\text{Ethyl-benzene}}{C_6H_5.C_2H_5}+HBr$$

$$\underset{\text{Toluene}}{C_6H_5.CH_3}+Cl.CH_3 = \underset{\text{Xylene.}}{C_6H_4(CH_3)_2}+HCl$$

By this method all the hydrogen atoms of benzene may be replaced in turn by alkyl groups, although it is often difficult to stop the action at the desired point and to separate the mixture of isomerides formed. The reaction is still further complicated by the fact that the aluminium chloride tends to detach the alkyl groups already introduced, and in the case of polyalkylated benzenes to promote molecular rearrangement into more stable isomerides.[3]

In spite of these drawbacks, however, the Friedel-Crafts reaction has proved of great value in the synthesis of benzene homologues and other aromatic compounds.

5. Benzene and its homologues may also be regenerated from the corresponding sulphonic acids by heating them with superheated steam

[1] Werner and Zilkens, *Ber.*, 1903, **36**, 2116, 3618. Houben, *Ber.*, 1903, **36**, 3083; 1904, **37**, 488. [2] Ferric chloride acts in a similar manner; Nencki, *Ber.*, 1897, **30**, 1766; 1899, **32**, 2414. [3] See G. Baddeley and J. Kenner, *J. C. S.*, 1935, 303.

in the presence of sulphuric acid, concentrated hydrochloric acid or phosphoric acid.

$$C_6H_3(CH_3)_2SO_3H+H_2O = C_6H_4(CH_3)_2+H_2SO_4$$

This reaction often provides a convenient method of separating a mixture of hydrocarbons. If, for example, one hydrocarbon can be sulphonated under certain conditions and another not, the latter can easily be extracted from the reaction mixture and the sulphonic derivative of the former then converted back into the hydrocarbon by the above means.

Properties and Reactions of the Alkyl-benzenes

The alkyl-benzenes are generally colourless liquids with a smell like that of benzene. They are insoluble in water but soluble in alcohol and ether. The introduction of a methyl group into the nucleus raises the boiling-points of the methyl-benzenes about 24° to 30°; if introduced into the side chain the rise is about 24°. Towards chlorine, bromine, sulphuric acid and concentrated nitric acid they behave like benzene, the hydrogen of the nucleus undergoing substitution.

A characteristic property of these hydrocarbons which is of great value for their identification is their behaviour on oxidation. Treatment with dilute nitric acid, chromic acid mixture, potassium permanganate, or ferricyanide converts each side chain into a carboxyl group (COOH), by the same intermediate steps as in the case of aliphatic compounds. From the number and relative positions of the resulting carboxyl groups it is possible to deduce the number and position of the alkyl radicals originally present.

Thus a hydrocarbon C_9H_{12} might have either of the constitutions

$C_6H_5.C_3H_7$	$C_6H_4\begin{matrix}CH_3\\C_2H_5\end{matrix}$	$C_6H_3(CH_3)_3$
Propyl- or isopropyl-benzene	One of the three methyl-ethylbenzenes	One of the three trimethyl-benzenes.

On oxidation, the first compound yields benzoic acid, $C_6H_5.COOH$; each of the three methyl-ethyl-benzenes gives a different dicarboxylic acid, $C_6H_4(COOH)_2$, and each of the three trimethyl-benzenes a different tricarboxylic acid, $C_6H_3(COOH)_3$.

Toluene, *methyl-benzene*, $C_6H_5.CH_3$, occurs among the products of dry distillation of a number of substances, particularly of Tolu balsam (*Toluifera balsamum*), from which Berzelius first derived its name.

It may be obtained synthetically according to the foregoing methods, (1) by the action of sodium on a mixture of methyl iodide and bromo-benzene in dry ethereal solution, (2) by leading methyl chloride into benzene in the presence of aluminium chloride, (3) from phenyl magnesium bromide and dimethyl sulphate in dry ethereal solution, and (4) by the dry distillation of a mixture of sodium benzoate and sodium acetate. Toluene may also be prepared from toluene sulphonic acids and by the distillation of *p*-toluic acid.

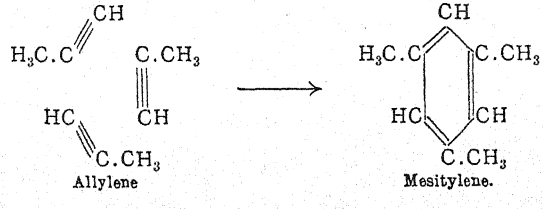
On the technical scale the only source of toluene is coal tar.

Toluene is a colourless, mobile and strongly refractive liquid, which freezes at —94° and boils at 110°; sp. gr. ·8841 at 0°. It is practically insoluble in water but it readily mixes with alcohol, ether and chloroform. It burns with a very smoky flame, dissolves sulphur, phosphorus, iodine, fats and resins, and is largely used as a solvent for phosgene. When oxidised with potassium bichromate and sulphuric acid, or with dilute nitric acid, toluene is converted into benzoic acid. On reduction it forms hexahydro-toluene. The behaviour of toluene towards chromyl chloride has been studied by Etard. In carbon disulphide solution a compound of the composition C_7H_8, $2CrO_2Cl_2$ is obtained, which decomposes with water to form benzaldehyde.

The action of chlorine on toluene varies with the temperature. At higher temperatures substitution occurs in the side chain, and at low temperatures in the nucleus. Chlorine passed into boiling toluene leads first to the formation of benzyl chloride, $C_6H_5.CH_2Cl$, which then yields benzal chloride, $C_6H_5.CHCl_2$, and finally benzo-trichloride, $C_6H_5.CCl_3$. In the cold, on the other hand, *o*- and *p*-chlorotoluenes, $C_6H_4Cl.CH_3$, are formed. On nitration, toluene yields a mixture of the three possible mono-derivatives, chiefly the *o*- and *p*-compounds, with a considerably smaller proportion of *m*-nitrotoluene.

Xylenes, *dimethyl-benzenes*, $C_6H_4(CH_3)_2$, are found in coal tar, the most valuable isomeride, *m*-xylene, being present in the greatest proportion. They are colourless liquids which distil at approximately the same temperature[1]; *o*-xylene boils at 142°, *m*-xylene at 139°, and *p*-xylene at 138°.

Trimethyl-benzenes, $C_6H_3(CH_3)_3$. Of these, hemimellitol (1 : 2 : 3) boils at 175°, pseudocumene (1 : 2 : 4) at 170°, and mesitylene (1 : 3 : 5) at 164°. All three occur in coal tar. Mesitylene is formed by the action of concentrated sulphuric acid on acetone or allylene, $3CH_3.CO.CH_3 = C_6H_3(CH_3)_3 + 3H_2O$.



Allylene — Mesitylene.

The proof of its symmetrical structure was of great importance in determining the orientation of benzene substitution products.

Cymene, p-*methyl-isopropyl-benzene*, $CH_3.C_6H_4.CH(CH_3)_2$ is found in various ethereal oils (oil of thyme and oil of eucalyptus), and may be obtained from camphor, oil of turpentine and certain other terpenes. It is a pleasant-smelling liquid, which boils at 175° and can be synthesised from *p*-bromo-isopropyl-benzene, methyl iodide and sodium.

Pentamethyl-benzene melts at 53° and boils at 230°.

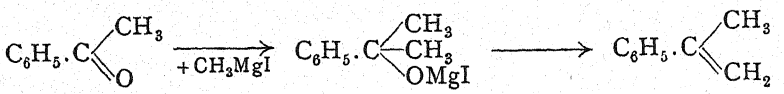
[1] These isomerides cannot be separated by distillation. For a method involving the use of sulphuric acid see *Ber.*, 1877, **10**, 1010; 1881, **14**, 2625; 1884, **17**, 444.

Hexamethyl-benzene may be prepared by leading an equimolecular mixture of methyl alcohol and acetone in the vaporous form over heated aluminium oxide.[1] It melts at 164° and boils at 264°.

Benzene Hydrocarbons with Unsaturated Side Chains

These show, on the one hand, the properties characteristic of aromatic compounds, and on the other those of the unsaturated hydrocarbons of the aliphatic series (see p. 118). They readily unite with hydrogen and halogens.

Alkylene benzene derivatives can be prepared by means of the Grignard reaction, either directly or by the elimination of water from the carbinols obtained in such variety by this reaction from aldehydes, ketones, esters and alkyl halides. Their direct formation occurs particularly in those cases where an excess of the Grignard reagent is employed, and the reaction mixture, after evaporation of the ether, is heated for some time,[2] *e.g.*,



Styrene, *phenyl-ethylene*, *vinyl-benzene*, $C_6H_5.CH:CH_2$, is the simplest representative of the olefin derivatives. It is present in storax and is a colourless, strongly refracting liquid, b.p. 146°, with a smell resembling that of benzene. It is obtained from cinnamic acid by heating with lime. It may be prepared from ethyl benzene,[3] $C_6H_5.C_2H_5 \longrightarrow C_6H_5.CH_2.CH_2Br \longrightarrow C_6H_5.CH:CH_2$, or by direct pyrolysis, $C_6H_5.C_2H_5 \longrightarrow C_6H_5.CH:CH_2+H_2$. At 200° it polymerises to a solid compound called metastyrene.[4] On reduction it yields ethyl-benzene, $C_6H_5.CH_2.CH_3$, and with bromine forms two isomeric dibromides, $C_6H_5.CHBr.CH_2Br$. Styrene is used in the manufacture of plastics (see index).

Phenyl-acetylene, $C_6H_5.C{\equiv}CH$, is a derivative of acetylene. It can be obtained by a variety of methods, such as from phenylpropiolic acid, $C_6H_5.C{\equiv}C.COOH$, by splitting off carbon dioxide, or from dibenzal-acetone tetrabromide by treatment with alcoholic potash.[5] It is a pleasant-smelling liquid, b.p. 142°, which like acetylene gives explosive metallic derivatives with ammoniacal silver nitrate or cuprous chloride solutions. When boiled with zinc dust and acetic acid, it takes up hydrogen and is converted into styrene, $C_6H_5.CH:CH_2$. Under the influence of dilute sulphuric acid, phenyl-acetylene combines with water to form acetophenone, $C_6H_5.CO.CH_3$.

[1] Reckleben and Scheiber, *Ber.*, 1913, **46**, 2363. [2] Klages, *Ber.*, 1902, **35**, 2633, 3506; 1904, **37**, 649, 1447. C. Hell, *Ber.*, 1904, **37**, 225, 230, 453, 1429, 4188. [3] J. v. Braun and Moldänke, *Ber.*, 1921, **54**, 618. [4] Stobbe, *Ann.*, 1909, **371**, 259. [5] G. Mühlhausen, *Ber.*, 1906, **39**, 4146.

IV

Halogen Derivatives of the Aromatic Hydrocarbons, and their Magnesium Compounds

Preparation.—Halogen-substitution products of the aromatic hydrocarbons can be prepared by the following methods.

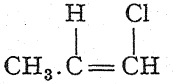
1. By the action of halogen on the hydrocarbon. In the case of iodine the hydriodic acid set free during the reaction must be removed as fast as it is formed. The hydrocarbon is therefore heated with iodine and an oxidising agent [1] such as mercuric oxide, iodic acid, or a persulphate. It has already been mentioned under toluene that chlorine and bromine may enter either the side chain or the nucleus, according to experimental conditions.

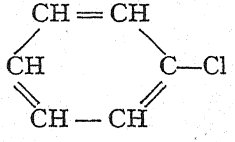
2. From the diazo-compounds (see p. 404) by interaction with cuprous chloride or bromide, or with potassium iodide.

$$C_6H_5N_2Cl = C_6H_5Cl + N_2$$

3. A simple method of brominating aromatic compounds [2] consists in shaking them at ordinary temperatures with an aqueous solution of hypobromous acid.

Properties.—In their chemical behaviour the aromatic halogen compounds are distinguished above all by the stability of the halogen atom directly attached to the nucleus. This halogen cannot be exchanged readily for other groups such as OH and NH_2, as in the saturated aliphatic derivatives, but resembles the relatively non-reactive halogen linked to an unsaturated carbon atom in an ethylene compound (p. 135). Never-





theless it should be noted that the entrance of further substituents into the molecule may increase the reactivity of the halogen in this sense; compounds which contain one or two nitro groups in the ortho-position to the halogen exchange the latter as readily as the alkyl halides [3]; similarly, the bromine in *o*-bromobenzoic acid is reactive (p. 374). In certain cases halogen attached directly to the nucleus may be brought into reaction by the use of catalysts or ultraviolet radiation.[4] In aromatic compounds such as benzyl chloride, $C_6H_5.CH_2Cl$, the halogen atom in the aliphatic side chain is comparatively reactive.

From the practical standpoint it is of considerable importance that aromatic halogen compounds resemble those of the aliphatic series in undergoing the *Grignard reaction*. When treated in dry ethereal solution

[1] K. Elbs and Jaroslawzew, *J. pr. Ch.* [2], 1913, **88**, 92. [2] O. Stark, *Ber.*, 1910, **43**, 670. [3] Kenner and collaborators, *J. C. S.*, 1914, **105**, 2717, and onwards. [4] K. W. Rosenmund, *Ber.*, 1923, **56**, 1950.

with metallic magnesium they form compounds of the general formula R. Mg. Hal. (see p. 136).

$$\underset{\text{Phenyl bromide.}}{C_6H_5Br} + Mg = \underset{\text{Phenyl magnesium bromide.}}{C_6H_5.Mg.Br}$$

$$\underset{\text{Benzyl chloride}}{C_6H_5CH_2.Cl} + Mg = \underset{\text{Benzyl magnesium chloride.}}{C_6H_5.CH_2.Mg.Cl}$$

Like the aliphatic organomagnesium halides, these have been employed with striking success in synthesis, and numerous examples of their use will be found in the following pages.

Iodine compounds containing the iodine atom in the nucleus possess the property of uniting with two atoms of chlorine to form iodochlorides, in which the iodine is trivalent. Aqueous sodium hydroxide converts these into iodoso-derivatives, the two chlorine atoms being replaced by one of oxygen.

$$\underset{\text{Iodobenzene.}}{C_6H_5.I} \xrightarrow{Cl_2} \underset{\text{Phenyl iodochloride}}{C_6H_5.ICl_2} \xrightarrow{H_2O} \underset{\text{Iodosobenzene.}}{C_6H_5.I{:}O}$$

Iodoso-compounds are yellow amorphous substances which behave as diacid bases, *e.g.* as $C_6H_5.I(OH)_2$; they combine with acids to form salts. With reducing agents, such as hydriodic acid, they lose oxygen and regenerate the iodo-compounds, a change which may also take place merely on heating (I). Oxidising agents convert iodoso- into iodoxy-compounds (II).

$$\text{I.} \quad \underset{\text{Iodosobenzene}}{2C_6H_5.IO} = \underset{\text{Iodoxybenzene}}{C_6H_5.IO_2} + \underset{\text{Iodobenzene.}}{C_6H_5.I}$$

$$\text{II.} \quad C_6H_5.IO + O = C_6H_5.IO_2$$

The iodoxy-compounds do not yield salts with acids, but resemble the iodoso-derivatives in decomposing violently when heated.

Chloro-, bromo- and iodo-benzene[1] are colourless liquids of characteristic odour, which boil at 132°, 157° and 188° respectively. **Hexachlorobenzene,** C_6Cl_6, is prepared by the exhaustive chlorination of benzene, and of many alkyl benzenes. It is a colourless crystalline substance, which melts at 226° and boils at 326°.

Chlorotoluene, $C_6H_4Cl.CH_3$, exists in three isomerides (*o*-, *m*- and *p*-), which may be obtained from the corresponding aminotoluenes or toluidines by way of the diazo-compounds. **Benzyl chloride,** $C_6H_5.CH_2Cl$, is formed by the action of chlorine on boiling toluene; it is a colourless liquid, b.p. 178°, which has a powerful irritant action on the eyes and nose. It is used in the preparation of benzyl derivatives. **Benzal chloride,** $C_6H_5.CHCl_2$, b.p. 207°, and **benzotrichloride,** $C_6H_5.CCl_3$, b.p. 213°, are formed by more prolonged action of chlorine on boiling toluene, and

[1] Iodobenzene can also be prepared from bromobenzene by converting it into phenyl magnesium bromide and subsequent treatment with iodine, $C_6H_5MgBr + I_2 = C_6H_5I + MgBrI$. Bodroux, *C. r.*, 1913, **135**, 1350.

are utilised industrially, the former in the preparation of benzaldehyde and the latter in that of benzoic acid. When the mixture of the two

$$\underset{\text{Benzal chloride}}{C_6H_5.CHCl_2} + Ca(OH)_2 = \underset{\text{Benzaldehyde.}}{C_6H_5.CHO} + CaCl_2 + H_2O$$

$$\underset{\text{Benzotrichloride}}{2C_6H_5.CCl_3} + 4Ca(OH)_2 = \underset{\text{Calcium benzoate.}}{(C_6H_5COO)_2Ca} + 3CaCl_2 + 4H_2O$$

chlorides, as obtained by chlorination, is heated with milk of lime, it yields benzaldehyde, calcium benzoate and calcium chloride. From this mixture benzaldehyde is removed by steam distillation, and benzoic acid is then precipitated from the residual calcium benzoate by means of hydrochloric acid.

Xylyl bromide, $CH_3.C_6H_4.CH_2Br$, and **xylylene bromide,** $CH_3.C_6H_4.CHBr_2$, are used as tear gases.

V

Nitrogen Derivatives of the Aromatic Hydrocarbons

In this section the technically valuable nitro- and amino-compounds are described first, followed by the intermediate products formed during the reduction of nitro- to amino-compounds. Chief among the latter are nitroso- and β-hydroxylamine derivatives and azoxy-, azo- and hydrazo-compounds. After these the diazo-compounds and hydrazines are treated, and finally the azo-dyes, which contain a variety of other groups in addition to nitrogen.

I—NITRO-COMPOUNDS

Preparation.—On account of their practical value the nitro-compounds are of outstanding importance. As has already been stated (p. 363), they are readily formed from aromatic hydrocarbons by the action of concentrated nitric acid.

$$C_6H_6 + HNO_3 = C_6H_5.NO_2 + H_2O$$

In a similar manner all kinds of aromatic derivatives, such as phenols, amines, aldehydes and acids, can be nitrated. The elimination of water is usually hastened by the addition of concentrated sulphuric acid to the nitric acid,[1] and the reaction may be carried out either by adding the substance to be nitrated to the mixture of acids, or by allowing nitric acid to run into a solution of the substance in sulphuric acid. The nitro-compounds can be isolated from the reaction mixture by dilution with water, in which they are generally insoluble or sparingly soluble.

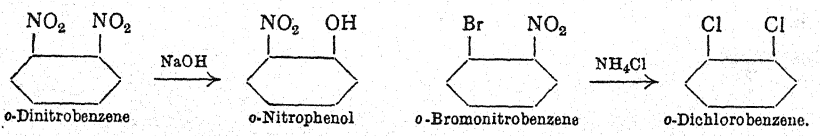
[1] A mixture of nitric acid and acetic anhydride has been found to be a very energetic nitrating agent. A. Pictet and Khotinsky, *Ber.*, 1907, 40, 1163.

A more recent method of nitration [1] makes use of liquid or gaseous nitrogen peroxide in the presence of aluminium chloride, an intermediate complex being formed, which for benzene has the composition $2AlCl_3$, $3N_2O_4$, $3C_6H_6$. Inorganic nitrates, such as sodium, potassium or bismuth nitrates, may also be employed for nitration.[2]

Although there is no difficulty in replacing all the hydrogen atoms in benzene with chlorine or bromine, it has not yet been found possible to effect the direct introduction of more than three nitro groups into benzene or its derivatives. In the alkyl benzenes, the more alkyl groups there are attached to the nucleus the more readily nitration proceeds. Where only one alkyl radical is attached to the ring, the nitro group tends to assume the ortho- or para- but not the meta-position. Thus toluene yields *o*- and *p*-nitrotoluenes, but little *m*-nitrotoluene. The presence of a hydroxyl group in the nucleus also exerts a directive influence towards the *o*- and *p*-positions, *e.g.* phenol gives *o*- and *p*-nitrophenols. On the other hand, in compounds containing the radicals —CHO, —COOH, or —CN, the nitro group tends to assume the meta-position. Similarly, when one nitro group is already present, a second generally enters in the meta-position.

Properties and Reactions.—The nitro-compounds are liquids or crystalline solids, the majority of which are yellow in colour. They are only very slightly soluble in water, but in organic solvents, such as alcohol and ether, they usually dissolve readily. Many of them are volatile in steam. Their boiling-points lie higher than those of the parent hydrocarbons. When treated with sodium or potassium alcoholates the almost colourless trinitrobenzenes form dark red addition compounds, the constitution of which has not yet been determined.[3] In the mono-substituted derivatives the nitro group is firmly united to the nucleus and cannot be directly exchanged for other atoms or groups. In the polynitro-compounds or halogen-substituted nitro-compounds, on the other hand, the nitro groups are more mobile, and one of them can often be replaced by other radicals.

o-Dinitrobenzene, for example, when boiled with alkali yields *o*-nitrophenol, and *o*-bromonitrobenzene gives *o*-dichlorobenzene when heated to 320° with ammonium chloride.[4]



o-Dinitrobenzene — *o*-Nitrophenol — *o*-Bromonitrobenzene — *o*-Dichlorobenzene.

Behaviour of the Nitro-compounds on Reduction

The behaviour of the aromatic nitro-compounds on reduction is of great practical and theoretical interest. When reduced by purely chemical

[1] A. Schaarschmidt, *Ber.*, 1924, **57**, 2065. [2] L. Spiegel and Haymann, *Ber.*, 1926, **59**, 202. [3] A. Hantzsch and Picton, *Ber.*, 1909, **42**, 2119. [4] J. Schmidt and Ladner, *Ber.*, 1904, **37**, 4403.

methods the final products, as in the case of the aliphatic derivatives, are amino-compounds.

$$C_6H_5NO_2+6H = C_6H_5.NH_2+2H_2O$$

The reaction, however, proceeds in several stages, and intermediate products are formed which may be isolated. One of the factors greatly influencing the course of reduction is the acidity or alkalinity of the solvent during the reaction. By the reduction of nitrobenzene in acid or neutral solution, Bamberger[1] showed that the **mononuclear intermediate products,** *nitrosobenzene* and *phenylhydroxylamine*, are first formed, and that these on further reduction yield aniline.[2]

$$\underset{\text{Nitrobenzene}}{C_6H_5.NO_2} \longrightarrow \underset{\text{Nitrosobenzene}}{C_6H_5.NO} \longrightarrow \underset{\beta\text{-Phenylhydroxylamine}}{C_6H_5.NHOH} \longrightarrow \underset{\text{Aniline.}}{C_6H_5.NH_2}$$

When the reduction is effected in alkaline solution the simpler products just described tend to interact with one another to give the more complex **dinuclear intermediate products,** *azoxybenzene*, *azobenzene* and *hydrazobenzene* :

$$\underset{\text{Nitrobenzene}}{C_6H_5.NO_2} \longrightarrow \underset{\text{Azoxybenzene}}{\begin{matrix}C_6H_5.N:O\\ \|\\ C_6H_5.N\end{matrix}} \longrightarrow \underset{\text{Azobenzene}}{\begin{matrix}C_6H_5.N\\ \|\\ C_6H_5.N\end{matrix}} \longrightarrow \underset{\text{Hydrazobenzene}}{\begin{matrix}C_6H_5.NH\\ |\\ C_6H_5.NH\end{matrix}} \longrightarrow \underset{\text{Aniline.}}{C_6H_5.NH_2}$$

Azoxybenzene is here produced by the condensation of nitrosobenzene with phenylhydroxylamine, according to the equation

$$C_6H_5NO+C_6H_5.NHOH = C_6H_5.N_2O.C_6H_5+H_2O$$

whilst the interaction between nitrobenzene and hydrazobenzene leads to the formation of azobenzene.[3]

Azobenzene is also produced from phenylhydroxylamine under the influence of alkali.

$$2C_6H_5.NHOH = C_6H_5.N_2.C_6H_5+2H_2O$$

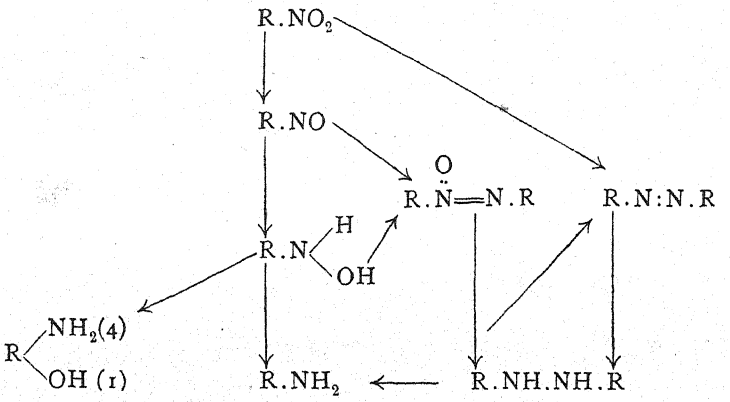
The course of the **electrolytic reduction** of aromatic mononitro-compounds has also been carefully investigated.[4] Once again employing nitrobenzene as our example, the main stages of the reduction in both alkaline and acid solution are: nitrobenzene ⟶ nitrosobenzene ⟶ phenylhydroxylamine ⟶ aniline. Secondary reactions, as before, play a considerable part. In weakly acid solution nitrobenzene gives aniline in good yield, but in strongly acid solution *p*-aminophenol is produced, owing to the *β*-phenylhydroxylamine undergoing intramolecular rearrangement.

$$\underset{\beta\text{-Phenylhydroxylamine}}{C_6H_5.NHOH} \longrightarrow \underset{p\text{-Aminophenol.}}{HO.C_6H_4.NH_2}$$

In an alkaline medium nitrosobenzene unites with *β*-phenylhydroxylamine, as described above, to form azoxybenzene, which reduces further to hydrazobenzene. The latter, by atmospheric oxidation, yields a little azobenzene, and on continued reduction is converted into aniline.

[1] E. Bamberger, *Ber.*, 1894, **27**, 1550. [2] As will be seen later, the oxidation of aniline to nitrobenzene represents the reverse of the above process. [3] E. Bamberger, *Ber.*, 1900, **33**, 271. [4] Haber, *Z. Elek.*, 1898, **4**, 511; *Z. phys. Ch.*, 1900, **32**, 271.

The various reactions taking place during the cathodic reduction of aromatic mononitro-compounds [1] have been expressed graphically as follows (Haber, *loc. cit.*) :—



In the above scheme the electrolytic reduction processes are indicated by perpendicular and horizontal arrows, and secondary changes by inclined arrows.

Description of the more important Nitro-Derivatives of the Benzene Series

Nitrobenzene, $C_6H_5.NO_2$, *oil of mirbane*, is prepared technically in very large quantities by allowing a nitrating acid, composed of 105 parts nitric acid and 160 parts sulphuric acid, to run slowly with continuous stirring into benzene contained in cast-iron cylinders. By suitable means the temperature is maintained first at 25°, and towards the end of the reaction is allowed to rise to 70° to 80°. The proportions employed are such that the nitric acid is almost completely used up, the sulphuric acid absorbing the water liberated. Nitrobenzene separates out in an upper layer above the denser acid, and is removed, washed with water and distilled in steam. A small quantity of *m*-dinitrobenzene, $C_6H_4(NO_2)_2$, remains behind. The lower layer of sulphuric acid is freed from nitric acid and organic matter, and then concentrated and used for further nitrations.

Nitrobenzene is a yellow, strongly refractive liquid, of sp. gr. 1·204 at 20°, which like benzaldehyde has a smell resembling that of bitter almonds. It boils at 208° and solidifies at 5·5°. Very dilute solutions of nitrobenzene in water have a decidedly sweet taste, and the vapour of the compound is poisonous when inhaled. Nitrobenzene is chiefly used in industry for the preparation of aniline, and also in the manufacture of perfumes and perfumed soaps.

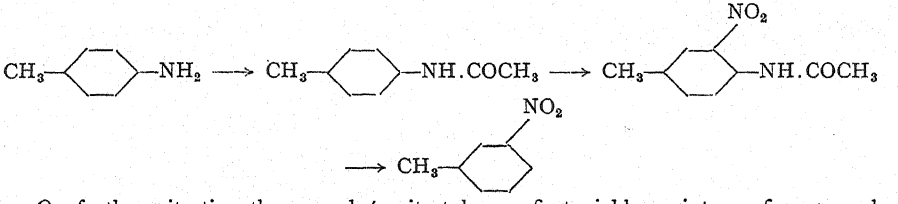
Dinitrobenzenes, $C_6H_4(NO_2)_2$. The nitration of benzene at higher temperatures yields m-*dinitrobenzene*, m.p. 90°, as chief product, together with small amounts of

[1] For the electrochemical reduction of aromatic dinitro- and polynitro-compounds see Brand, *Ber.*, 1905, **38**, 4006.

the *o*-compound (m.p. 116°) and *p*-compound (m.p. 172°). The first of these serves for the production of *m*-nitraniline and *m*-phenylene diamine, which are used in the dye industry, and is also a component of certain explosives.

Sym- or **1 : 3 : 5-Trinitrobenzene,** $C_6H_3(NO_2)_3$, m.p. 121°, is formed by heating benzene to 140° with a mixture of nitric and fuming sulphuric acids.

Nitrotoluene, $CH_3.C_6H_4.NO_2$. Toluene on nitration yields a mixture of *o*- and *p*-nitrotoluenes containing a little of the *m*-compound. These can be separated by fractional distillation. o-*Nitrotoluene*, b.p. 218°, gives *o*-nitrobenzaldehyde on oxidation and is also used in the preparation of *o*-nitrobenzyl chloride and *o*-toluidine. It exists in two isomeric forms,[1] a labile α-modification, m.p. −9·4°, and a stable β-modification, m.p. −3·6°. p-*Nitrotoluene*, b.p. 230° and m.p. 54°, is converted by the action of fuming sulphuric acid into *p*-nitrotoluene-*o*-sulphonic acid, which is used in the preparation of the dyestuff Direct Yellow. Pure m-*nitrotoluene*, m.p. 16°, b.p. 230°, is best prepared indirectly by nitration of *p*-acetotoluidide and subsequently removing the acetylamino group by hydrolysis and diazotisation (see p. 401).



On further nitration the *o*- and *p*- nitrotoluenes first yield a mixture of 2 : 4- and 2 : 6-dinitrotoluenes and finally T.N.T. or s-**trinitrotoluene.** The last is a valuable explosive. *Amatol* is an explosive containing a mixture of T.N.T. with ammonium nitrate.

2 : 4 : 6 - Trinitro - *tert* - butyl - toluene, $C_6H[NO_2, NO_2, NO_2, CH_3, C(CH_3)_3 = 2:4:6:1:3]$, m.p. 97°, smells powerfully of musk and is brought on to the market as *artificial musk* (mixed with 80 per cent. acetanilide). It is obtained by the nitration of butyl toluene (prepared from isobutyl chloride, toluene and aluminium chloride).

II.—AMINO DERIVATIVES OF BENZENE

The aromatic amines may be derived theoretically from ammonia in the same manner as the aliphatic amines. In the true aromatic derivatives the nitrogen is attached directly to the benzene nucleus, as in $C_6H_5.NH_2$ and $NH_2.C_6H_4.CH_3$. When, however, the amino group is linked to a carbon atom of the side chain in an alkyl benzene, as in the case of $C_6H_5.CH_2.NH_2$, we are dealing with a substituted aliphatic amine, with properties like those of the alkyl amines. The true aromatic amines undergo many of the reactions given by the fatty amines (pp. 170 *et seq.*) but differ from the latter in a number of points. For example, the aromatic derivatives are weaker bases than those of the aliphatic series, owing to the acidic character of the phenyl group. In addition, primary and tertiary aromatic amines differ from the corresponding aliphatic compounds in their behaviour towards nitrous acid.

1. Primary Monamines

Methods of Formation.—(1) The primary aromatic amines are almost always prepared by reducing the corresponding nitro-compounds.

$$C_6H_5NO_2 + 6H = C_6H_5NH_2 + 2H_2O$$

[1] E. Knoevenagel, *Ber.*, 1907, **40**, 508.

This can be effected in various ways, such as by the use of zinc and hydrochloric acid, tin or stannous chloride and hydrochloric acid, iron and hydrochloric acid, alcoholic ammonium sulphide, or by electrochemical methods. In many cases reduction may be carried out very conveniently at ordinary temperatures by use of hydrogen and *Raney nickel catalyst*,[1] which is prepared by boiling nickel-aluminium alloy with alkali, when the aluminium dissolves, leaving nickel in a finely divided and highly active state. The intermediate products which are formed under different conditions have already been described in detail in the foregoing pages.

(2) Amines may be obtained from phenols by heating them to 150° with the double compound of zinc chloride and ammonia, ($ZnCl_2$, NH_3), *e.g.* $C_6H_5OH+NH_3 = C_6H_5NH_2+H_2O$. The substitution of an amino-group for a phenolic hydroxyl group or a halogen atom attached to a benzene nucleus takes place more readily when nitro-groups are also present in the compounds. Sulphonic acids, in many cases, can be transformed into amines by heating with sodamide.[2]

(3) A rapid and efficient method[3] of converting an aromatic carboxylic acid into a primary amine is to treat the acid, dissolved in concentrated sulphuric acid at 45-55°, with a solution of hydrazoic acid in chloroform, the addition being made drop by drop over a period of two hours with stirring. Alternatively, the sulphuric acid solution may be covered with a layer of chloroform and concentrated aqueous sodium azide (about 20 per cent. excess) added slowly under the same conditions. The mixture is finally run on to ice. Yields by this method are usually very high.

$$C_6H_5.COOH+N_3H = C_6H_5.NH_2+N_2+CO_2$$

(4) Among other methods of preparing higher homologues of aromatic amines may be mentioned one discovered by A. W. Hofmann. When aniline is heated to a high temperature with alkyl halides, an N-alkyl derivative is first formed, which changes by intramolecular rearrangement into a mixture of nuclear-substituted anilines. The procedure recommended by Hofmann is to start with the hydrochlorides of secondary or tertiary fatty-aromatic amines, or the quaternary ammonium salts, and to heat in closed vessels at a temperature of 250° to 300°. Ethyl-aniline hydrochloride, for example, undergoes the following change :

$$\begin{matrix} C_6H_5 \\ C_2H_5 \end{matrix}\!\!>\!NH, HCl \longrightarrow \begin{matrix} C_6H_4.NH_2, HCl \\ | \\ C_2H_5. \end{matrix}$$

By this means Hofmann prepared an aniline derivative in which all five hydrogen atoms of the ring were replaced by methyl groups :

$$(CH_3)_3C_6H_2.N(CH_3)_2, HI \longrightarrow (CH_3)_5C_6.NH_2, HI$$

It should be noted that this reaction is not only of scientific interest,[4] but is also of great practical value. It is employed on the technical scale for the production of the aniline homologues required in the dyestuff industry.

[1] See, for example, A. Albert and B. Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1940, **74**, 74. [2] F. Sachs, *Ber.*, 1906, **39**, 3006. [3] K. F. Schmidt, *Ber.*, 1924, **57**, 704. The reaction should be carried out under the draught, as breathing the vapour of hydrazoic acid, even in traces, leads to severe headache. [4] A similar *migration of alkyl groups* has been observed with derivatives of other cyclic bases, such as pyridine, pyrazine, pyrrole and pyrazole. For the mechanism of this change, which is assumed to involve the separation of the alkyl group as a positive ion, see H. B. Watson, *A. R.*, 1939, 204.

Properties and Reactions.—The primary monamino-compounds are colourless liquids or solids, which are volatile with steam and can be distilled without decomposition. As already mentioned, they are weak bases which do not give an alkaline reaction. With the entrance of electro-negative groups such as Cl and NO_2 into the nucleus, the basic character becomes still weaker, and the salts of these substituted anilines are either dissociated with water or incapable of existence. From the chemical point of view the primary aromatic amines resemble the fatty compounds in their behaviour towards alkylating agents, acid chlorides, aldehydes and chloroform (see p. 133). They differ mainly in their reaction with nitrous acid, which in acid solution converts them into diazo-compounds. In the amino-benzenes the nuclear hydrogen is far more readily substituted than in benzene itself, and in the same way the amines are much more susceptible to oxidation than the hydrocarbons. The various products obtained by the above reactions are described in detail under aniline.

According to conditions, bromine may react with aromatic amines at the ordinary temperature to form substitution or addition compounds. A study of this reaction has revealed a number of interesting regularities in connection with substitution.[1]

Aniline and its Derivatives

Aniline, *phenylamine*, $C_6H_5.NH_2$, is prepared technically from nitrobenzene. The latter is mixed with a little water in a cast-iron vessel provided with stirring apparatus and a reflux condenser. Steam is led in to warm the mixture, to which iron filings and hydrochloric acid are then added. Only a small proportion (about $\frac{1}{40}$) of the amount of acid required by the first equation is needed in actual practice, because the ferric chloride formed undergoes hydrolysis to ferric hydroxide and hydrochloric acid. The latter again reacts with iron with the result that

$$C_6H_5NO_2 + 2Fe + 6HCl = C_6H_5NH_2 + 2FeCl_3 + 2H_2O$$
$$2FeCl_3 + 6H_2O \rightleftharpoons 2Fe(OH)_3 + 6HCl$$

a small amount of acid acts as a carrier in the reduction by iron and water. At the end of the reaction milk of lime is added, in order to decompose the aniline hydrochloride formed, and the free aniline is distilled over in steam and fractionated *in vacuo*. For the intermediate stages in this reduction see p. 388.

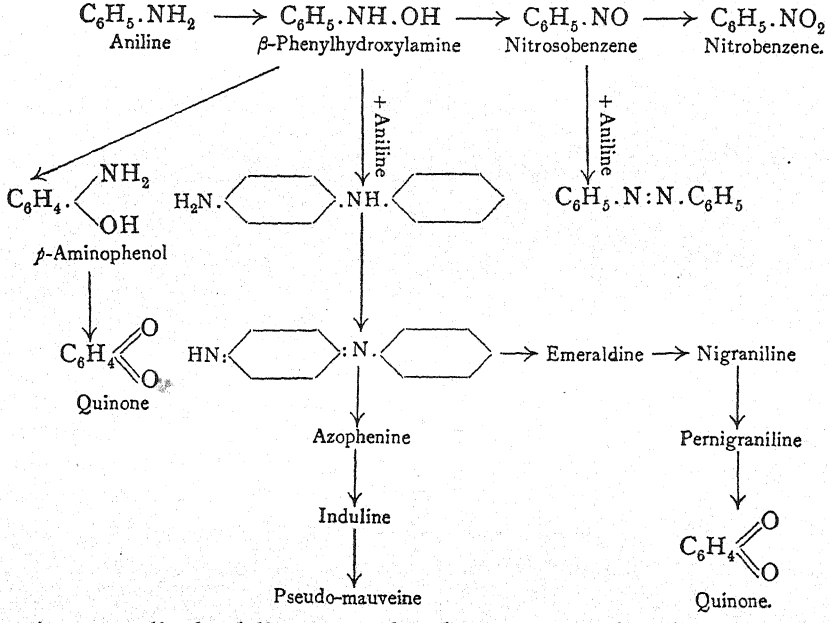
When reduced with concentrated hydrochloric acid and other metals, nitrobenzene yields aniline containing chloraniline. The proportion of the latter has been found to vary from 3 per cent. with tin to 26 per cent. using zinc.[2]

In the pure state aniline is a colourless, strongly refractive liquid of sp. gr. 1·024 at 16°, which boils at 189° and solidifies at −8°. It is only sparingly soluble in water and is poisonous.

Aniline is easily attacked by oxidising agents, the products obtained depending very much on the conditions of experiment. They may be

[1] See K. Fries, *Ann.*, 1906, **346**, 128. [2] G. R. Robertson and R. A. Evans, *J. Org. Chem.*, 1940, **5**, 142.

conveniently classified as *mononuclear oxidation products*, such as phenylhydroxylamine, nitrobenzene and quinone; *dinuclear products*, such as azobenzene, azoxybenzene and quinone-diimine; and those which may be termed *polynuclear*, such as emeraldine and aniline black, which result from further chain formation and secondary reactions.[1] The genetic connection between these various products of reaction is summarised in the following table,[2] in which the series in the first line, connected by horizontal arrows, is exactly the reverse of that given on p. 388 for the reduction of nitrobenzene.



An exceedingly delicate test for the presence of aniline consists in treating it in aqueous solution with a solution of bleaching powder (Runge), when a deep violet coloration is produced, which changes rapidly to a dirty red tint. Another characteristic reaction of aniline is the formation of a deep blue or black colour (aniline black) when potassium bichromate is added to a solution of the base in sulphuric acid.

Halogens readily yield substitution derivatives with aniline. Bromine, for example, converts it into **2 : 4 : 6-tribromo-aniline,** a reaction which may be used for the quantitative estimation of aniline. By interaction with sulphur, aniline forms a diamino-diphenyl sulphide, $(NH_2.C_6H_4)_2S$, m.p. 108°, in which the amino-groups occupy the *p*-positions to the sulphur atom.

The most important salt of aniline is the readily soluble hydrochloride, $C_6H_5.NH_2$, HCl, known technically as *aniline salt*. The sulphate $(C_6H_5.NH_2)_2H_2SO_4$ is only sparingly soluble in water.

Aniline reacts with aromatic aldehydes with elimination of water to form *Schiff's* bases or **anils.**

$$C_6H_5.CHO + H_2N.C_6H_5 = C_6H_5.CH:N.C_6H_5 + H_2O$$

Benzylidene-aniline.

[1] Willstätter, *Ber.*, 1907, **40**, 2665; 1909, **42**, 2147, 4118. [2] S. Goldschmidt, *Ber.*, 1920, **53**, 28.

If the hydrogen atoms of the amino-group in aniline are replaced by organic acid radicals, compounds termed **anilides** are produced. These can be prepared by heating aniline salts with the required organic acids, or by the interaction of aniline and an acid chloride or ester. The best known example of this class is acetanilide.

Acetanilide, $C_6H_5.NH.CO.CH_3$, may be prepared by heating acetic acid with aniline or aniline acetate.

$$CH_3COOH+NH_2.C_6H_5 = CH_3CO.NH.C_6H_5+H_2O$$

It melts at 112°, boils at 304°, and is only very sparingly soluble in cold water, from which it crystallises in small white plates. Acetanilide is employed in medicine as a febrifuge under the name of *antifebrin*.

Nitration of Aniline

Nitric acid reacts vigorously with aniline, converting it into resinous products. Hence, in order to obtain mono- and dinitro-derivatives, the amino-group must first be protected. This can be done either by acetylating the aniline before nitration, or by nitrating it with a mixture of nitric acid and much sulphuric acid. In the latter case all three isomeric mono-nitro-compounds are formed together, viz., *o*-**nitraniline,** m.p. 71°, *m*-**nitraniline,** m.p. 114°, and *p*-**nitraniline,** m.p. 147°; whereas when the aniline is first acetylated the *p*-nitro-compound is the chief product.[1] These nitranilines can also be prepared by the partial reduction of the corresponding dinitrobenzenes by means of ammonium sulphide.

Carbonic Acid Derivatives of Aniline

The anilides of carbonic acid correspond to the urethanes and may be obtained in a similar manner to these (see p. 337).

Phenyl-urethane, $C_6H_5.NH.CO.OC_2H_5$, can be prepared by the action of aniline on chlorocarbonic ester. **Carbanilide** or *sym. diphenyl-urea*, $(C_6H_5.NH)_2CO$, m.p. 235°, and *phenyl-urea*, $C_6H_5.NH.CO.NH_2$, m.p. 144°, are obtained by special methods, *e.g.* from aniline sulphate and potassium cyanate, or by heating aniline with urea. **Phenyl isocyanate,** $C_6H_5.N:C:O$, b.p. 166°, can be prepared by treating aniline or its hydrochloride with phosgene, or by distilling phenyl-urethane with phosphorus pentoxide. It is a colourless liquid, the vapour of which has a lachrymatory action. Phenyl isocyanate has often been employed in the examination of tautomeric compounds, particularly for showing the presence of a hydroxyl group. The interaction of equimolecular quantities of phenyl isocyanate and a hydroxy derivative leads to the formation of a *phenyl-carbamic ester*, according to the equation:

$$R.OH+\ddot{C}:N.C_6H_5 = RO—\ddot{C}—NH.C_6H_5$$

Later research, however, has shown that this substance is not a reliable reagent for the hydroxyl group.[2] Under the influence of various substances phenyl isocyanate polymerises to triphenyl isocyanate, m.p. 274°. In contact with water it yields diphenyl-urea.

Thiocarbanilide, diphenyl-thiourea, $(C_6H_5NH)_2CS$, is prepared by boiling aniline with carbon disulphide.

$$CS_2+2H_2NC_6H_5 = H_2S+CS(NHC_6H_5)_2$$

It is obtained in the form of colourless plates, m.p. 154°. When heated with concentrated hydrochloric acid it decomposes into aniline and phenyl isothiocyanate (phenyl mustard oil), $C_6H_5.N:C:S$, a colourless liquid of pungent smell.

[1] A. F. Holleman, *Ber.*, 1911, **44**, 704. [2] See Dieckmann, Hoppe and Stein, *Ber.*, 1904, **37**, 4627. Michael, *Ber.*, 1905, **38**, 22. H. Goldschmidt, *Ber.*, **38**, 1896.

Monamino Derivatives of Toluene

Toluidines, $CH_3.C_6H_4.NH_2$.—The ortho and para derivatives are obtained by reducing the corresponding nitrotoluenes with iron and hydrochloric acid, and are employed in the manufacture of azo- and triphenyl methane dyestuffs. *o*-Toluidine is a liquid, b.p. 197°, and *p*-toluidine a solid which melts at 45° and boils at 198°. *m*-Toluidine can be prepared from *m*-nitrotoluene (obtained by indirect methods, see p. 389) and is a liquid, b.p. 199°.

Benzylamine, $C_6H_5.CH_2.NH_2$, b.p. 183°, which may be regarded as a phenyl-substituted methylamine, is formed by the methods described under aliphatic amines, *e.g.* by heating benzyl chloride, $C_6H_5.CH_2Cl$, with ammonia, or by the reduction of phenyl nitro-methane, $C_6H_5.CH_2.NO_2$. It is a colourless liquid, and in its chemical properties resembles methylamine. It dissolves in water to give a strongly alkaline solution and yields no diazo-compound with nitrous acid.

2. Secondary Monamines

Purely aromatic secondary amines may be prepared by heating the primary bases with their hydrochloric acid salts. For example, by heating aniline with aniline hydrochloride at 220° to 230° in an autoclave, **diphenylamine,** $(C_6H_5)_2NH$, is formed.

$$C_6H_5NH_2, HCl + H_2NC_6H_5 = HN(C_6H_5)_2 + NH_4Cl$$

Another method of preparing compounds of this type is by the action of bromobenzene on primary aromatic amines, in the presence of a trace of cuprous iodide as catalyst.[1] Diphenylamine is a colourless crystalline substance, m.p. 54° and b.p. 310°, which is used in the preparation of diamino-diphenylamine and azo-dyes. Its basic properties are so weak that its salts are decomposed with water. On the other hand, the hydrogen of the imino-group is replaceable by metals. With nitrous acid it yields diphenylnitrosamine, $(C_6H_5)_2N.NO$.

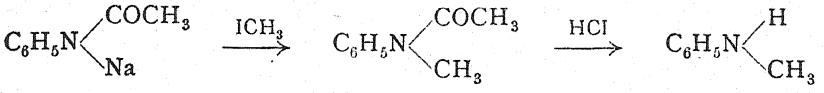
Diphenylamine is rapidly attacked by oxidising agents, yielding a product which gives an intense blue coloration with concentrated sulphuric acid. Hence it is employed for the qualitative detection of nitric and nitrous acids. This behaviour is due to the formation of tetraphenyl-hydrazine, which gives the above striking colour reaction with concentrated sulphuric acid.[2]

$$\underset{\text{Diphenylamine}}{2(C_6H_5)_2NH} \xrightarrow{O} \underset{\text{Tetraphenyl-hydrazine.}}{(C_6H_5)_2N{-}N(C_6H_5)_2} + H_2O$$

Secondary *mixed aromatic amines* or phenyl-alkylamines may be prepared from the alkyl iodides and the acetyl derivatives of primary aromatic bases.[3] **Methylaniline,** for example, is formed in this manner

[1] I. Goldberg, *Ber.*, 1907, **40**, 4541. [2] Wieland, *Ber.*, 1906, **39**, 1499. E. Weitz and H. W. Schwechten, *Ber.*, 1927, **60**, 1203. [3] For details of preparation from aromatic amines and alkyl bromide see W. J. Hickinbottom, *J. C. S.*, **1930**, 992.

by the action of methyl iodide on the sodium salt of acetanilide, and subsequent removal of the acetyl group by hydrolysis :



The secondary mixed aromatic amines are stronger bases than the purely aromatic compounds. When treated with nitrous acid they yield nitroso derivatives, $C_6H_5N(R).NO$, which with weak reducing agents are converted into hydrazines, $C_6H_5N(R).NH_2$, and on energetic reduction regenerate the original secondary amine.

3. Tertiary Monamines

In this case also a distinction must be drawn between compounds of purely aromatic and those of mixed aliphatic-aromatic nature. A point of outstanding interest is the behaviour of phenyl-dialkylamines towards nitrous acid. Whereas tertiary aliphatic amines do not react with nitrous acid at all, mixed amines of the above type are transformed by this reagent into *p*-nitroso-compounds (see below). A small proportion of a nitro derivative is also formed as a by-product.

Tertiary phenylamines either fail to react with nitrous acid or undergo nitration in the nucleus.

Triphenylamine, $(C_6H_5)_3N$, can be obtained by the action of bromobenzene on dipotassium aniline, $C_6H_5NK_2+2C_6H_5Br = (C_6H_5)_3N+2KBr$. It melts at 127° and forms no salts with acids.

Dimethylaniline, $C_6H_5N(CH_3)_2$, is formed by the methylation of aniline, and is prepared industrially by heating aniline hydrochloride with methyl alcohol in an autoclave.

$$C_6H_5NH_2, HCl+2CH_3OH = C_6H_5.N(CH_3)_2, HCl+2H_2O$$

The resulting hydrochloride of dimethylaniline is treated with milk of lime, and the free base removed by distillation in steam. It is an oil of peculiar smell, boiling at 192°. With dry hydrogen chloride the base yields a mono- and a di-hydrochloride, both of which readily lose hydrochloric acid.[1] A number of the characteristic reactions of dimethylaniline depend on the extraordinary mobility of the hydrogen atom in the para-position. Thus with nitrous acid it gives ***p*-nitrosodimethylaniline,** $(NO)C_6H_4.N(CH_3)_2$, crystallising in green leaves or plates, m.p. 85°. The hydrochloride of the nitroso-base crystallises in yellow needles, melting at 177°. When *p*-nitroso-dimethylaniline is reduced with zinc dust it yields *p*-amino-dimethylaniline, $NH_2.C_6H_4.N(CH_3)_2$, which, like the nitroso-compound, is used in the manufacture of numerous dyes.

Dimethylaniline condenses with aldehydes in such a manner that the

[1] R. Scholl and Escales, *Ber.*, 1897, **30**, 3134.

para-hydrogen atoms of two molecules of the base unite with the aldehydic oxygen to form water :

$$H.CH{:}O + 2C_6H_5N(CH_3)_2 = H_2C\begin{matrix}{}^{1}C_6H_4{}^{4}N(CH_3)_2 \\ {}_{1}C_6H_4{}_{4}N(CH_3)_2\end{matrix} + H_2O$$

Formaldehyde Dimethylaniline Tetramethyl-diamino-diphenylmethane.

Acid chlorides react in a similar way,

$$COCl_2 + 2C_6H_5N(CH_3)_2 = CO\begin{matrix}{}^{1}C_6H_4.{}^{4}N(CH_3)_2 \\ {}_{1}C_6H_4.{}_{4}N(CH_3)_2\end{matrix} + 2HCl$$

Phosgene Dimethylaniline Michler's ketone.

When treated with an aqueous solution of hydrogen peroxide, dimethylaniline takes up an atom of oxygen to form a product of the formula $C_6H_5.N(CH_3)_2 \rightarrow O$, known as *dimethylaniline oxide*, from which oxygen can readily be removed to give the original base.

This behaviour towards hydrogen peroxide is peculiar to all aromatic amines of the type $Ar.N(Alk)_2$.

4. Diamines and Polyamines

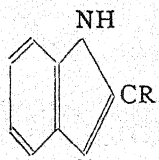
Aromatic diamines may be prepared by the reduction of the corresponding dinitro-, nitroamino-, or aminoazo-compounds.

For example, m-**phenylene diamine,** $C_6H_4(NH_2)_2$, m.p. 63° and b.p. 287°, is obtained by the reduction of *m*-dinitrobenzene with zinc dust and caustic soda, and o-**phenylene diamine,** m.p. 102° and b.p. 252°, in a similar manner from *o*-nitraniline. p-**Phenylene diamine,** m.p. 147° and b.p. 267°, is prepared by reducing aminoazobenzene with tin and hydrochloric acid.

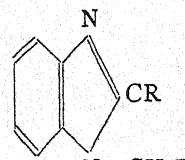
$$C_6H_5.N:N.C_6H_4.NH_2 + 4H = C_6H_5.NH_2 + H_2N.C_6H_4.NH_2$$

The diamines are solid compounds of strong basic properties. Their reactions differ according to the positions of the amino groups.

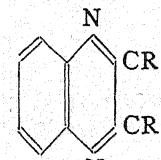
o-**Diamines** are distinguished by the ease with which they condense with a variety of other compounds to form cyclic derivatives. Thus when heated with organic acids they yield iminazoles, with aldehydes they yield aldehydines, and with 1 : 2-diketones they yield quinoxalines.



Iminazoles



Aldehydines



Quinoxalines.

The quinoxaline reaction[1] is useful as a qualitative test for *o*-diamines as well as for 1 : 2-diketones.

***m*-Diamines** when treated with nitrous acid give brown dyes—aminoazo-compounds—produced by the condensation of several molecules of the diamine (*Bismarck brown* reaction). The *p*-substituted ***m*-diamines** do not give this colour test.

In neutral or dilute mineral acid solution *m*-diamines may be coupled with diazotised aniline to form diaminoazo-compounds known as *chrysoidines*.

The most important reactions of the ***p*-diamines** are the following. With oxidising agents, *e.g.* when boiled with manganese dioxide and sulphuric acid, they readily pass into quinones, which may be recognised by their penetrating odour.

$$\underset{p\text{-Phenylene diamine}}{C_6H_4(NH_2)_2} + H_2O + O = \underset{\text{Quinone.}}{C_6H_4O_2} + 2NH_3$$

By the action of ferric chloride on *p*-diamines in the presence of hydrogen sulphide, there are formed blue, violet, or crimson red dyestuffs, which contain sulphur. Mixtures of *p*-diamines with phenols yield on oxidation dark blue *indophenol* dyestuffs. Similarly, the oxidation of mixtures of *p*-diamines and primary monamines at the ordinary temperature leads to the formation of highly-coloured *indamines*, and at higher temperatures of *safranines*.

Amines containing three or more amino groups in the nucleus very readily undergo oxidation, and their instability increases with the number of such groups present.

III.—NITROSO- AND β-HYDROXYLAMINE DERIVATIVES

Mononitroso derivatives of the aromatic hydrocarbons are obtained, in general, by the action of certain oxidising agents (cold monopersulphuric acid, or potassium bichromate and sulphuric acid) on the corresponding amino-compounds : $Ar.NH_2 \longrightarrow Ar.NH.OH \longrightarrow Ar.NO$. Like the aliphatic nitroso derivatives (see p. 163), they are very volatile and exist in different molecular states. The solid aromatic nitroso-compounds are colourless and bimolecular, but in solution, or when fused, the great majority of them assume a blue or green colour and give molecular weights corresponding to the monomolecular formula Ar.NO. On further oxidation the nitroso-compounds readily pass into nitro-compounds, and on reduction they yield amino-compounds.

The typical aromatic representative of this class, **nitrosobenzene**, $C_6H_5.NO$, is obtained by oxidising β-phenylhydroxylamine with potassium bichromate and sulphuric acid. It is also formed when aniline is oxidised (*a*) in sulphuric acid solution with potassium permanganate, in the presence of a little formaldehyde, (*b*) with monopersulphuric acid

[1] O. Hinsberg, *Ann.*, 1887, **237**, 327, 342.

(*Caro*). It crystallises in colourless volatile needles, m.p. 68°, and possesses a powerful characteristic smell. In the molten state or in solution it is emerald green in colour. It is readily oxidised to nitrobenzene or reduced to aniline. Nitrosobenzene condenses with aniline to form azobenzene, and with β-phenylhydroxylamine to form azoxybenzene (see p. 399).

β-Arylhydroxylamines are prepared by reducing aromatic nitro-compounds with neutral reagents such as zinc dust and ammonium chloride solution, or ammonium sulphide. They are also obtained by electrochemical reduction, in which case a cathode solution of acetic acid and sodium acetate dissolved in water or other solvent is best employed.[1] They readily reduce ammoniacal silver solutions and Fehling's solution, and when dissolved in water rapidly take up oxygen from the air, particularly in the presence of alkali. Those β-arylhydroxylamines in which the *p*-hydrogen atom is not substituted are transformed by sulphuric acid into the isomeric *p*-amino-phenols (see below).

β-Phenylhydroxylamine, $C_6H_5.NHOH$, is obtained by reducing nitrobenzene by the above methods. It is a white crystalline compound, m.p. 81°. The powdered substance induces violent sneezing. Atmospheric oxygen converts it into azoxybenzene, and with more energetic oxidising agents it yields nitrosobenzene. It reduces Fehling's solution and ammoniacal silver nitrate, even in the cold. With acids it combines to form salts, and when warmed with mineral acids is readily isomerised to *p*-aminophenol.

$$C_6H_5.NH.OH \longrightarrow HO.C_6H_4.NH_2$$

Nitrous acid converts it into a nitroso derivative, $C_6H_5N(NO)OH$. This *nitrosophenyl-hydroxylamine* is more conveniently obtained by the action of nitric oxide on an ethereal solution of phenyl magnesium bromide:

$$NO \longrightarrow O{:}N.N{:}O \longrightarrow O{:}N.N\begin{matrix}\diagup OMgBr\\ \diagdown C_6H_5\end{matrix} \longrightarrow O{:}N.N\begin{matrix}\diagup OH\\ \diagdown C_6H_5\end{matrix}$$

Diphenyl-hydroxylamine,[2] $(C_6H_5)_2N.OH$, is prepared by treating nitrosobenzene with phenyl magnesium bromide:

$$C_6H_5.NO + C_6H_5.MgBr \xrightarrow{+H_2O} (C_6H_5)_2N.OH + MgBrOH$$

It is a beautifully crystalline compound which melts with decomposition at 60°, and is of interest in connection with the discovery of divalent nitrogen derivatives.

Nitrogen diphenyl, $(C_6H_5)_2N$, and other diaryl derivatives of divalent nitrogen, are formed as a result of the dissociation of tetra-aryl hydrazines.[3] Nitrogen diphenyl bears the same relationship to diphenyl-hydroxylamine as nitric oxide to nitrous acid.

$(C_6H_5)_2N$	$(C_6H_5)_2N.OH$	$(C_6H_5)_2N:O$
$O:N$	$O:N.OH$	$O:N:O$

The presence of nitrogen diphenyl in a solution of tetraphenyl-hydrazine can be detected by its unsaturated properties. When, for example, nitric oxide is passed into

[1] Haber, *Z. Elek.*, 1897-98, 4, 506; 5, 77. K. Brand, *Ber.*, 1905, **38**, 3076. [2] H. Wieland, *Ber.*, 1912, 45, 494. [3] H. Wieland, *Ann.*, 1911, **381**, 201; 1912, **392**, 156; 1913, **401**, 233; *Ber.*, 1912, 45, 2600.

a solution of the hydrazine in toluene at 90° diphenyl nitrosamine is formed, produced by union of the two divalent nitrogen groups.

$$(C_6H_5)_2N + NO \longrightarrow (C_6H_5)_2N.NO$$

The dissociation of tetraphenyl-hydrazine into the free radical $(C_6H_5)_2N$ is exactly analogous to the formation of triphenyl methyl from hexaphenyl-ethane, which will be discussed later.

$$(C_6H_5)_2N.N(C_6H_5)_2 \longrightarrow 2(C_6H_5)_2N$$
$$(C_6H_5)_3C.C(C_6H_5)_3 \longrightarrow 2(C_6H_5)_3C$$

Another compound which tends to dissociate in solution into a derivative of divalent nitrogen is *hexaphenyl-tetrazane.*[1] In the solid state this is monomolecular, but in solution it largely exists as *triphenylhydrazyl.*

$$(C_6H_5)_2N{-}\underset{\displaystyle H_5C_6}{\underset{|}{N}}{-}\underset{\displaystyle C_6H_5}{\underset{|}{N}}{-}N(C_6H_5)_2 \rightleftharpoons 2(C_6H_5)_2N{-}\underset{\displaystyle C_6H_5}{\underset{|}{N}}{-}$$

Diphenyl-nitric oxide[2] $(C_6H_5)_2N{:}O$, is obtained from diphenyl-hydroxylamine by oxidation with silver oxide: $(C_6H_5)_2N.OH \longrightarrow (C_6H_5)_2N{:}O$. It is an analogue of nitrogen dioxide (see above) from which it is derived by the replacement of an oxygen atom by two benzene residues. It crystallises in deep red needles, m.p. 62°, and in many ways resembles NO_2. Like the latter it shows a characteristic band spectrum, and its colour in solution resembles that of gaseous NO_2, but is of a deeper red. It unites with other radicals such as nitric oxide, nitrogen dioxide and triphenyl methyl. With NO it forms $(C_6H_5)_2N(:O).NO$, which then undergoes intramolecular rearrangement to give *p*-nitro-diphenylamine, $O_2N.C_6H_4.NH.C_6H_5$. The first stage of this reaction is comparable to the formation of N_2O_3 from NO and NO_2.

IV.—AZOXY-, AZO- AND HYDRAZO-COMPOUNDS

The azoxy-compounds are generally prepared by heating nitro derivatives with an alcoholic solution of sodium methoxide; sodium amalgam, or magnesium and ammonium chloride solution, can also be employed as the reducing agent. They are yellow or red in colour, crystallise well, and on further reduction yield azo-, hydrazo- and amino-compounds. With moderately warm concentrated sulphuric acid they isomerise to *hydroxy-azo-compounds.*

Azoxybenzene, $C_6H_5.\overset{\displaystyle O}{\overset{\cdot\cdot}{N}}{=}N.C_6H_5$, is best prepared by boiling nitrobenzene with a methyl alcoholic solution of sodium methoxide.

$$4C_6H_5.NO_2 + 3CH_3.ONa = 2C_6H_5.\overset{\displaystyle O}{\overset{\cdot\cdot}{N}}{:}N.C_6H_5 + 3H.COONa + 3H_2O$$
(Sodium formate.)

It forms pale yellow crystals, m.p. 36°. When warmed with concentrated sulphuric acid it isomerises into *p*-hydroxy-azobenzene.[3]

$$C_6H_5.N{:}\overset{\displaystyle O}{\overset{\cdot\cdot}{N}}.C_6H_5 = C_6H_5.N{:}N.C_6H_4.OH$$

Azoxy-compounds were formerly believed to possess the symmetrical structure, *e.g.*

$C_6H_5.\overset{\displaystyle O}{\overset{/\quad\backslash}{N}}{-}{-}N.C_6H_5$. An unsymmetrical azo-compound, however, was shown by

[1] S. Goldschmidt and co-workers, *Ber.*, 1920, **53**, 44; 1922, **55**, 616; *Ann.*, 1924, **437**, 194. [2] H. Wieland, *Ber.*, 1914, **47**, 2111; 1920, **53**, 210; 1922, **55**, 1798. [3] Wallach, *Ber.*, 1880, **13**, 525; 1881, **14**, 2617. Bamberger, *Ber.*, 1900, **33**, 3192. In the above case a small amount of the *o*-compound is also formed.

Angeli to give rise in some instances to two isomeric azoxy-compounds. The symmetrical formula has therefore been abandoned.

$$C_6H_5.N:N.C_6H_4Br \begin{cases} \nearrow C_6H_5.N(:O):N.C_6H_4Br \\ \searrow C_6H_5.N:N(:O).C_6H_4Br \end{cases}$$

The unsymmetrical structure has also been conclusively proved by polarimetric methods.[1]

Azo-compounds may be obtained from nitro-compounds by reduction with sodium amalgam or an alkaline solution of stannous chloride, from azoxy-compounds by cautious heating with iron filings, and from hydrazo-compounds by oxidation. As will be seen later, aminoazo-compounds, the amino derivatives of azo-compounds, are formed when hydrochlorides of aromatic amines are warmed with diazoamino-compounds.

The azo-compounds are red to yellowish-red crystalline substances, which on further reduction yield first hydrazo-compounds and finally amines. They are very stable and may be distilled without decomposition, differing in this respect from the unstable diazo-compounds to be described later, which contain two nitrogen atoms united with one hydrocarbon radical and an acidic atom or group (*e.g.* $C_6H_5.N_2.Cl$).

Azobenzene, $C_6H_5.N:N.C_6H_5$, is prepared by distilling azoxybenzene with iron filings. It forms orange-red crystals, m.p. 68° and b.p. 295°.

$$C_6H_5.N(:O):N.C_6H_5+Fe = C_6H_5.N:N.C_6H_5+FeO$$

In ordinary azobenzene the phenyl groups are arranged in the *trans* positions with respect to the two nitrogen atoms, as is proved by the zero value of the dipole moment. Under the influence of light, especially in the ultra-violet region, the *trans* form in solution is partly converted into the *cis* isomeride (15-40 per cent.), which has a dipole moment of 3·0. *Cis* azobenzene forms bright red crystals, which melt at 71·4° and at this temperature change comparatively rapidly into *trans* azobenzene.[2] The two isomerides are conveniently separated by chromatographic adsorption on alumina.[3] An interesting chemical difference is that whereas the *trans* compound does not react as such with diphenyl ketene, the latter combines vigorously with *cis* azobenzene at ordinary temperatures. The structure of the adduct is shown by its decomposition at 190° to yield both azobenzene and benzophenone-anil.[4]

$$\begin{matrix} Ph.N \\ \| \\ Ph.N \end{matrix} + \begin{matrix} CPh_2 \\ \| \\ CO \end{matrix} \longrightarrow \begin{matrix} Ph.N—CPh_2 \\ \quad | \quad | \\ Ph.N—CO \end{matrix} \xrightarrow{190°} \begin{matrix} Ph.N:N.Ph \\ \text{and} \\ Ph_2C=N.Ph \end{matrix}$$

Hydrazo-compounds, R.NH.NH.R, are produced by the reduction of azo-compounds with ammonium sulphide, zinc dust and alcoholic potash, sodium amalgam, or sodium amylate. They may also be prepared directly from nitro-compounds by reduction with zinc dust and alkali, or by electrochemical means.

The hydrazo-compounds, which may be regarded as symmetrical derivatives of hydrazine, $NH_2.NH_2$, are *colourless* neutral substances,

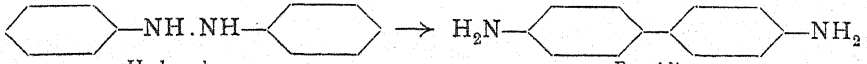
[1] T. T. Chu and C. S. Marvel, *J. A. C. S.*, 1933, **55**, 2841. [2] G. S. Hartley, *J. C. S.*, 1938, 633. [3] A. H. Cook and D. G. Jones, *J. C. S.*, 1939, 1309. [4] Cook and Jones, *ibid.*, 1941, 184.

which are readily oxidised to azo-compounds. In the presence of mineral acids they undergo a peculiar intramolecular change (see below).

Hydrazobenzene, $C_6H_5.NH.NH.C_6H_5$, forms colourless leaves or plates, m.p. 131°, is very easily oxidised to azobenzene, and with energetic reducing agents yields aniline. When heated, it decomposes into azobenzene and aniline.

$$2C_6H_5.NH.NH.C_6H_5 = C_6H_5.N{:}N.C_6H_5 + 2C_6H_5.NH_2$$

Under the influence of mineral acids hydrazobenzene undergoes a remarkable intramolecular change, the chief product of the reaction being a base known as *benzidine* or 4 : 4′-diamino-diphenyl.

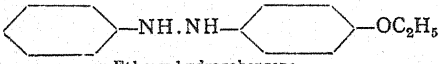


Hydrazobenzene. Benzidine.

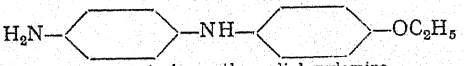
Consequently, when hydrazobenzene is formed by the reduction of azobenzene in acid solution, it is immediately transformed into benzidine. The latter is prepared technically by reducing nitro-benzene to hydrazobenzene by means of zinc dust and sodium hydroxide, and treating the product with acid. Benzidine and its homologue tolidine are of value in the preparation of substantive dyes.

The intramolecular change described above is also undergone by other hydrazo-compounds in which the two para-positions are not substituted, and is known generally as the *benzidine transformation*. A small amount of 4 : 2′-diaminodiphenyl is also formed (*diphenyline transformation*).

It is obvious that this change cannot take place in the same manner if one of the two para-hydrogen atoms of the hydrazo-compound is already replaced by a substituent. The course of the reaction in this case was carefully examined by Jacobson and his co-workers.[1] It results in a semi-benzidine or *semidine transformation*, the products being called semidines, *e.g.*,



p-Ethoxy-hydrazobenzene.



p-Amino-*p*-ethoxy-diphenylamine.

V.—DIAZO-COMPOUNDS[2] AND HYDRAZINES

The aromatic diazo-compounds containing the group —N_2— are of great importance theoretically as well as practically. They were discovered in 1860 by Griess, as a result of the action of nitrous acid on primary amines of the benzene series. Not only do they afford interesting examples of isomerism, but they are highly reactive and form the starting-

[1] P. Jacobson, *Ann.*, 1895, **287**, 97; 1898, **303**, 290. [2] See *The Aromatic Diazocompounds*, by K. H. Saunders (Arnold, 1936).

point in the preparation of a large number of dye-stuffs. Since diazobenzene hydroxide may play the part of a base, an acid, or an indifferent substance, it is not surprising that chemical opinion as to the constitution of the diazo-compounds passed through many phases [1] prior to the researches of Hantzsch and of Bamberger.

According to Hantzsch, the diazo-compounds ArN_2X (where Ar is C_6H_5 or a derivative thereof) may be divided into the following classes, the existence of which is largely dependent on the chemical character of the group X :

(*a*) Compounds of the structure $\overset{\text{Ar.N.X}}{\underset{\text{N}}{\vdots\vdots}}$, such as the *diazonium salts*, *e.g.* $C_6H_5N_2Cl$, which resemble ammonium salts in character.

(*b*) Compounds of the structure Ar.N : N.X. These are *diazo-compounds* comparable to the azo-derivatives, and sometimes occur in two stereoisomeric forms, viz. :

1. *Syn-diazo-compounds* of the type $\overset{\text{Ar.N}}{\underset{\text{X.N}}{\vdots\vdots}}$, which are produced in the first instance, but owing to their extremely labile nature have only been isolated in a few cases.

2. *Anti - diazo - compounds* of the structure $\overset{\text{Ar.N}}{\underset{\text{N.X.}}{\vdots\vdots}}$

These are stable substances.

The diazonium salts are by far the most important of the above derivatives, and will therefore be treated in most detail.

1. Diazonium Salts

Preparation.—If the diazonium salts are only required in solution, their preparation is exceedingly simple. A well-cooled aqueous solution of a salt of a primary aromatic amine, containing at least one equivalent of free mineral acid, is treated with the calculated amount of sodium nitrite dissolved in water. Free nitrous acid is liberated, and *diazotisation* proceeds as in the following equation :

$$\underset{\text{Aniline hydrochloride}}{C_6H_5NH_2.Cl} + NO_2H = \underset{\text{Benzene diazonium chloride.}}{C_6H_5N_2.Cl} + 2H_2O$$

The resulting diazonium salt remains in solution and may be employed directly for the production of other compounds, such as azo-dyes. This method of diazotisation is carried out on a very large scale industrially.

Owing to the high solubility of most of the diazonium salts in water, and the ease with which they undergo decomposition, a different method has to be adopted for the

[1] Compare Hantzsch, *Ahrens Sammlung*, VIII, 1902, pp. 1 to 82.

preparation of the salts in the solid state. For this purpose an alcoholic solution of the amine is treated with the requisite acid, and amyl nitrite added to the cooled mixture. The salt either separates out immediately or is thrown out by the addition of ether. Generally it is even more convenient to diazotise in glacial acetic acid solution. It is only in rare instances that the diazonium salt requires to be isolated in the pure state in this manner.

Properties.—Diazonium salts are usually colourless crystalline substances, which are readily soluble in water, less soluble in alcohol, and in the dry state explode violently when heated or struck. In every respect they are genuine salts, comparable to the ammonium and especially to the quaternary ammonium salts. Diazonium nitrates and chlorides are neutral in aqueous solution, and the conductivity figures show them to be ionised to about the same extent as the corresponding potassium and ammonium salts. The resemblance to ammonium salts is also exhibited in the formation and character of complex compounds, such as chloroplatinates, aurochlorides, mercury double salts and diazonium silver cyanides :

$$(ArN_2)_2PtCl_6,\ (ArN_2)AuCl_3,\ (ArN_2)HgCl_3,\ (ArN_2)Ag(CN)_2$$

Diazonium hydroxides, $ArN_2.OH$, have been obtained in solution only, by treating the diazonium chlorides with silver oxide or the sulphates with barium hydroxide. They are very unstable substances, which are proved to be genuine hydroxyl bases [1] by their conductivity and the speed with which they bring about hydrolysis. In this respect their strength varies between that of ammonia and that of the alkali hydroxides.

Reactions of the Diazonium Salts

These reactions are used in the preparation of a great variety of benzene derivatives. Many of them depend on the ease with which diazonium salts, or the neutral diazo-compounds with which they are in equilibrium, decompose with *elimination of nitrogen*, the place of which is then taken by other atoms or groups. It is believed that this decomposition results in the liberation of a highly reactive *aryl radical*, *e.g.* phenyl, C_6H_5, which rapidly attacks any molecule in its neighbourhood. For further details see p. 406.

(1) *Replacement of N_2-group by hydroxy-, alkoxy-, or acyloxy-groups.* The interaction of diazonium salts with hydroxy-compounds—on warming with water, alcohol, or acetic acid—leads to the formation of phenol or its derivatives as the chief product [2] of reaction, and may be formulated in the case of benzene diazonium chloride in the following manner (intermediate phases being omitted) :

$$\underset{\substack{\text{Benzene}\\\text{diazonium chloride}}}{C_6H_5N_2Cl}+H_2O = \underset{\text{Phenol.}}{C_6H_5.OH}+N_2+HCl$$

$$C_6H_5N_2Cl+H.OCH_3 = \underset{\text{Anisole.}}{C_6H_5.OCH_3}+N_2+HCl$$

[1] Hantzsch and Davidson, *Ber.*, 1898, **31**, 1612. [2] Hantzsch and Thompson, *Ber.*, 1908, **41**, 3519.

(2) *Replacement of the N_2-group by hydrogen* occurs as a by-reaction in the above decomposition with alcohol.[1] In the case of negatively substituted diazonium salts this becomes the main reaction. Tribromobenzene diazonium salts, for example, yield almost exclusively tribromobenzene, even with very dilute aqueous alcohol.

$$\underset{\text{Tribromobenzene diazonium chloride}}{C_6H_2Br_3.N_2Cl} + C_2H_5OH = \underset{\text{Tribromobenzene}}{C_6H_3Br_3} + N_2 + HCl + \underset{\text{Acetaldehyde.}}{CH_3.CHO}$$

Other reducing agents, such as alkaline stannous chloride solution, also replace the nitrogen group by hydrogen.

(3) *Replacement of the N_2-group by iodine* occurs on merely warming a solution of a diazonium iodide. The reaction is often employed as a preparative method, since many iodo-compounds are thus obtained in good yield.

$$\underset{\text{Benzene diazonium iodide}}{C_6H_5.N_2.I} = \underset{\text{Iodobenzene.}}{C_6H_5.I} + N_2$$

(4) *Replacement of the N_2-group by chlorine, bromine, or cyanogen.* It is not possible to introduce these substituents into the benzene ring in the manner described under (3) above. Sandmeyer,[2] however, discovered that the change could be effected with the aid of the corresponding cuprous salts. When solutions of the diazonium salts are heated in the presence of cuprous chloride, bromide, or cyanide, there are formed chloro- bromo-, or cyanobenzenes (*Sandmeyer reaction*).

$$C_6H_5.N_2.Cl = C_6H_5.Cl + N_2$$
$$C_6H_5.N_2.Br = C_6H_5.Br + N_2$$
$$C_6H_5.N_2.CN = C_6H_5.CN + N_2$$

The Sandmeyer reactions depend in part on the union of the diazo-compound with cuprous salts to form double compounds, which are very easily decomposed.

The most important of these reactions is the conversion of diazonium salts into cyano-compounds (benzonitriles), from which the corresponding acids are readily obtained by hydrolysis. This is a valuable method for the synthesis of aromatic acids.

A modification of the above is the *Gattermann reaction*.[3] The cuprous salts are here replaced by copper powder, which in the main appears to act catalytically.

Diazonium borofluorides decompose on warming to form the corresponding aryl fluoro-compounds,[4] $Ar.N_2.(BF_4) \longrightarrow Ar.F + N_2 + BF_3$.

As diazonium salts are readily prepared from nitro-compounds by way of the amines, the reactions just described are frequently employed in the laboratory for converting aromatic nitro-compounds into the corresponding hydroxy-, chloro-, bromo-, cyano- and other derivatives.

[1] Hantzsch, *Ber.*, 1901, **34**, 3337; 1903, **36**, 2061. [2] Sandmeyer, *Ber.*, 1884, **17**, 2650; 1887, **20**, 1495; 1890, **23**, 1630, 1880. [3] *Ber.*, 1890, **23**, 1218; 1892, **25**, 1086. [4] G. Balz and G. Schiemann, *Ber.*, 1927, **60**, 1186.

Nitro-compounds thus form a valuable means of passing from an aromatic compound to its various derivatives.

In addition to these remarkable reactions of the diazonium salts, there are also other important changes which proceed *without elimination of nitrogen.*

(1) Diazonium bromides add on bromine to form perbromides, and these by treatment with ammonia yield diazoimides, which may be regarded as derivatives of hydrazoic acid.

$$C_6H_5N_2Br \xrightarrow{+Br_2} C_6H_5N_2Br_3 \xrightarrow{+NH_3} \underset{\text{Benzene diazoimide.}}{C_6H_5.N_3} + 3HBr$$

(2) On reduction, diazonium salts are converted into monosubstituted hydrazines (see p. 410).

(3) Reactions of the highest importance are those which lead to the *production of azo-dyes from diazonium salts*, by the " coupling " of the latter with amines and phenols. These are dealt with under the heading of azo-dyes (p. 412).

2. Diazo-Compounds, Ar.N:NX

When a diazonium salt is treated with alkalis it is converted into a metallic salt or diazotate of the formula $Ar.N_2.OM$, in which the diazo-hydroxide plays the part of an acid, *e.g.*,

$$C_6H_5.N_2Cl + 2KOH = \underset{\substack{\text{Potassium benzene}\\ \text{diazotate.}}}{C_6H_5.N{:}N.OK} + KCl + H_2O$$

These diazotates can exist in two isomeric modifications, which are colourless and possess many properties in common. Both are readily reduced to hydrazines, and with benzoyl chloride yield nitrosobenzanilides. On oxidation both are converted into nitramine salts, *e.g.* $Ar.N_2O.ONa$. They differ mainly in the relative speeds with which they undergo reaction. For example, the labile diazotates first formed couple with phenols in alkaline solution to give azo-dyes, whereas the stable diazotates obtained by the more prolonged action of alkalis on diazonium salts either fail to give this reaction or react very slowly. With mineral acids the diazotates are transformed back into diazonium salts. Hantzsch has proved that these diazotates are structurally similar and that their differences are due to stereoisomerism, as illustrated in the following formulæ :

$C_6H_5.N$ ‖ $KO.N$	$C_6H_5.N$ ‖ $N.OK$
Syn-diazotate ; labile and couples readily	Anti-diazotate ; stable and couples very slowly or not at all.

According to this view both *syn-* and *anti-diazohydroxides* are to be regarded as stereoisomeric oximes of nitrosobenzene. Experiment has

shown that both forms are actually produced by the interaction of hydroxylamine and nitrosobenzene.

$$Ar.N:O+H_2N.OH \xrightarrow{KOH} Ar.N:N.OK+H_2O$$

In this reaction labile syn-forms are first obtained, which then pass into the stable anti-modifications.[1]

Stereoisomerism of a similar type has also been found to exist in the case of the diazo-sulphonates, $Ar.N:N.SO_3K$, and the diazo-cyanides, $Ar.N:N.CN$. These are obtained from diazonium salts by the action of potassium sulphite and potassium cyanide respectively.

$$\underset{\text{Diazonium salt}}{Ar.N_2X}+K.SO_3K = \underset{\text{Diazo-sulphonate}}{Ar.N_2.SO_3K}+KX$$

$$Ar.N_2X+KCN = \underset{\text{Diazo-cyanide.}}{Ar.N_2.CN}+KX$$

The stable anti-diazocyanides are converted into the labile and reactive syn-forms by exposure to light.[2] Confirmation of the conclusion of Hantzsch that the stable compounds are of the anti-configuration has now been obtained by dipole moment determinations, the values being small compared with those of the syn-forms.[3]

Relationship between Nitrosamines and Diazo-Compounds

Primary Nitrosamines and Anti-diazohydroxides.—The group $-N_2OH$ in the compounds $R.N_2OH$ is tautomeric, functioning either as an anti-diazohydroxide ($-N:N.OH$) or as a primary nitrosamine structure ($-NH.NO$). According to the researches of Hantzsch and his co-workers,[4] all the metallic salts, $R.N_2OM$, are to be regarded as anti-diazotates, but the free hydrogen derivatives may exist either as diazohydrates, $R.N:N.OH$, or, as more frequently happens, as primary nitrosamines, $R.NH.NO$. Hence, in the latter case, during the conversion of the salt (diazotate) into the hydrogen compound, an intramolecular rearrangement takes place, $Ar.N:N.OK \longrightarrow Ar.NH.NO$. Conversely, the primary phenyl nitrosamines behave as pseudo-acids, reacting with alkalis to form salts of the anti-diazohydrate structure. The anti-diazotates are thus closely related to the nitrosamines.

The isolation of both isomeric forms of the hydrogen compound from one and the same tautomeric substance has been effected in a few instances, *e.g.* in the case of 2 : 4 : 6-tribromobenzene anti-diazohydrate, $C_6H_2Br_3.N:N.OH$, and the corresponding nitrosamine,[5] $C_6H_2Br_3.NH.NO$. These isomerides recall the somewhat similar aliphatic nitroso-compounds, $R_2CH.NO$ and $R_2C:N.OH$, and their formation is analogous to that of the isomeric nitro-compounds (pp. 164 and 165). In chemical behaviour the isomerides differ in accordance with the formulæ given above. The anti-diazohydrates resemble reactive hydroxy acids, whereas the nitrosamines are indifferent pseudo-acids.

Liberation of Free Radicals during the Decomposition of Diazonium Salts and Diazocompounds[6]

Hantzsch assumed that the decomposition of a diazonium salt in water was dependent on its partial hydrolysis to form the diazonium hydroxide,

[1] Hantzsch, *Ber.*, 1905, **38**, 2056. [2] O. Stephenson and W. A. Waters, *J. C. S.*, 1939, 1796. [3] R. J. W. Le Fèvre and H. Vine, *ibid.*, 1938, 41. [4] *Ber.*, 1899, **32**, 1703; 1900, **33**, 2188. [5] Hantzsch and Pohl, *Ber.*, 1902, **35**, 2964. [6] For further details see D. H. Hey and W. A. Waters, *Chem. Rev.*, 1937, **21**, 169.

which then entered into equilibrium with the isomeric *syn*- and *anti*-diazohydroxides. Of these, the *syn*-diazohydroxide was supposed to be highly unstable, rapidly breaking down to give a phenol and nitrogen.

$$[C_6H_5.\overset{+}{N}\equiv N]\overset{-}{Cl} + H_2O \rightleftharpoons [C_6H_5.\overset{+}{N}\equiv N]\overset{-}{OH} + HCl$$

$$C_6H_5.OH + N_2 \longleftarrow C_6H_5.N(HO.N) \rightleftharpoons C_6H_5.N(N.OH)$$

In the presence of an alcohol the reactive *syn*-diazohydroxide was represented as combining with the alcohol to form an addition compound, which then disrupted to yield a hydrocarbon, alkoxy-derivative or other product.

These views have recently been modified and extended by later discoveries. Benzene diazonium chloride has long been known to react with methyl and ethyl alcohols, for example, the main changes being expressed as follows :

$$C_6H_5.N_2Cl + CH_3OH \longrightarrow C_6H_5.OCH_3 + N_2 + HCl$$
$$C_6H_5.N_2Cl + CH_3.CH_2OH \longrightarrow C_6H_6 + N_2 + CH_3.CHO + HCl.$$

But despite the striking dissimilarity of these processes, the two reactions have been found to occur with the same velocity [1] as measured by the rate of evolution of nitrogen. Higher alcohols also react with the same velocity as methyl and ethyl alcohols. It is very unlikely that the intermediate products required by the above mechanism of Hantzsch would all decompose at the same rate, and a new explanation has now been advanced which links up the reactions of diazonium salts and diazo-compounds with those of the nitrosoacylarylamines, *e.g.* nitrosoacetanilide, $C_6H_5.N(NO).COCH_3$.

According to modern views, the diazonium salt, or more probably its covalent tautomer (*e.g.* $C_6H_5.N{:}N.X$), slowly breaks down with loss of nitrogen and liberation of a free phenyl or other aryl radical. The latter

$$C_6H_5.N{:}N.Cl \longrightarrow C_6H_5. + N_2 + Cl$$

is exceedingly reactive and immediately attacks any molecule in its neighbourhood. The part of the change which determines the observed rate of reaction is therefore the *slow* decomposition of the diazo-compound, which is a unimolecular reaction and largely independent of the medium in which it occurs.

Waters [2] allowed dry benzene diazonium chloride to decompose under acetone and showed that benzene and chloracetone were formed. The

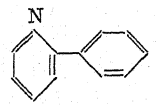
$$C_6H_5.N_2Cl + CH_3.CO.CH_3 \longrightarrow C_6H_6 + CH_3.CO.CH_2Cl + N_2$$

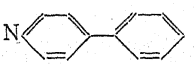
phenyl radical on being set free immediately attacks the acetone, removing hydrogen to give benzene. The production of chloracetone indicates the liberation of a neutral active form of chlorine, since the chlorine anion is stable and non-reactive.

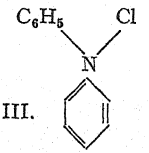
[1] Pray, *J. Phys. Chem.*, 1926, 1477. [2] W. A. Waters, *J. C. S.*, 1937, **113**, 2007, 2014.

Liberation of active chlorine was also proved by adding metals such as Sb, Bi, Pb and Hg, when these were also attacked and converted into chlorides (even in the presence of excess calcium carbonate, which would have neutralised any hydrogen chloride). It is therefore concluded that phenyl diazonium chloride decomposes into the neutral products, $C_6H_5\cdot$, $Cl\cdot$ and N_2.

Further confirmation of the neutrality of the disruption products is afforded by the observation that dry phenyl diazonium chloride interacts with pyridine to give 2- and 4-phenylpyridines [1] (I and II).

I. 

II. 

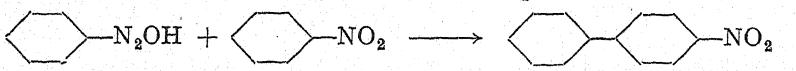
III. 

If the diazonium chloride reacted as such it would be expected to break down into a positively charged phenyl group and negatively charged chlorine, which would combine with pyridine to form the quaternary salt III. Since this does not occur, the diazonium salt must therefore first undergo transformation into the neutral covalent benzene diazochloride, before decomposing into a phenyl radical, nitrogen and neutral chlorine.

Another set of reactions which is believed to be dependent on the formation of free radicals is the decomposition of diazohydroxides in the presence of aromatic liquids. Gomberg [2] diazotised aromatic amines, using the minimum amount of water, and added benzene or another aromatic liquid followed by a 20 per cent. solution of sodium hydroxide. Rapid reaction set in, which led to the formation of a diaryl, *e.g.*

$$C_6H_5.N_2OH+C_6H_5Br \longrightarrow \underset{\text{2- and 4-bromodiphenyls.}}{C_6H_5.C_6H_4Br}+N_2+H_2O$$

This change is also more readily explained on the assumption that free phenyl radicals are liberated by the disruption of the diazohydroxide. A curious feature is that the usual laws of benzene substitution do not hold for the reactions with free radicals, para derivatives being obtained from nitrobenzene and benzonitrile [3] in which the normal directive power of the nitro or cyano substituent is to the meta position.



4-Nitrodiphenyl.

Similar results have been obtained in the decomposition of nitroso-acylarylamines. For example, nitrosoacetanilide (prepared by the action of N_2O_3 on acetanilide dissolved in acetic acid) reacts with benzene to form diphenyl (*Bamberger*).

$$C_6H_5.N(NO).COCH_3+C_6H_6 \longrightarrow C_6H_5.C_6H_5+N_2+CH_3.COOH$$

It has been shown by Bamberger, Hantzsch and others that nitroso-acetanilide is tautomeric with benzene anti-diazoacetate, because the

[1] Möhlau and Berger, *Ber.*, 1893, **26**, 1994. [2] *J. A. C. S.*, 1924, 2339; 1926, 1372.
[3] Compare the formation of 2- and 4-phenylpyridines from pyridine described above.

compound obtained by the action of N_2O_3 on acetanilide is the same as that produced by the acetylation of sodium benzene diazohydroxide :

$$Ph.NH.CO.CH_3 \xrightarrow{N_2O_3} Ph.N(NO).COCH_3 \longleftrightarrow Ph.N:N.O.COCH_3 \xleftarrow{Ac_2O} Ph.N:N.ONa$$

It would therefore not be unexpected if the reactions undergone by nitroso-acetanilide (benzene diazoacetate) resembled those given above for the diazohydroxides.

Proof that the reactions are the same has been provided by Grieve and Hey.[1] The nitroso compound has been shown to interact with toluene, chlorobenzene, nitrobenzene and benzaldehyde to give in each case the corresponding 4-substituted diphenyl. Moreover, these changes all proceed with the same velocity, despite the different nature of the substituent groups present. The reaction is therefore expressed as follows :

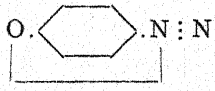
$$C_6H_5.N(NO).COCH_3 \longrightarrow C_6H_5\cdot + N_2 + CH_3\cdot COO\cdot$$
$$C_6H_5\cdot + C_6H_5R \longrightarrow p\text{-}C_6H_5.C_6H_4R + H\cdot$$
$$CH_3\cdot COO\cdot + H\cdot \longrightarrow CH_3.COOH$$

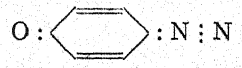
Although the free phenyl radical thus displaces hydrogen in an *aromatic* ring to form a diaryl, the reaction with an *aliphatic* organic compound takes place in a different manner. Waters [2] finds that dry nitrosoacetanilide decomposes in the presence of hexane, cyclohexane, ether, dioxan, acetone, ethyl acetate or acetic anhydride with the production of benzene ($C_6H_5\cdot + RH \longrightarrow C_6H_6$, compare reaction of benzene diazonium chloride with ethyl alcohol). On the other hand, aliphatic halogen derivatives such as alkyl halides, chloroform or carbon tetrachloride are attacked with the formation of a halogenated benzene ($C_6H_5\cdot + C_2H_5Br \longrightarrow C_6H_5Br$).

Diazohydroxides, Diazoanhydrides and Quinone-diazides. Sensitiveness of Diazo-Compounds towards Light

When diazonium chloride solutions are treated with a small excess of silver oxide there are obtained solutions of the very unstable diazonium hydroxides, *e.g.* $C_6H_5N_2OH$. The normal (*syn*-) metallic diazotates on careful addition of acetic acid do not yield the hydrates, but deposit the corresponding *diazoanhydrides* [3] (*diazo-oxides*).

Hydroxyphenyl diazonium salts, containing the OH group in the *o*- or *p*-position, on treatment with alkalis form internal anhydrides of the diazonium type (I) or of the quinone type (II).

I. 

II. 

Hence they are described as quinone-diazides.[4]

[1] *J. C. S.*, 1934, 1797. [2] *J. C. S.*, 1937, 113. [3] E. Bamberger, *Ber.*, 1896, **29**, 459.
[4] L. Wolff, *Ann.*, 1900, **312**, 126. H. Staudinger, *Helv. Chim. Acta*, 1922, **5**, 87.

Owing to their sensitiveness to light, diazo-compounds are now being used in the manufacture of photographic tracing paper.[1] In the earlier process the paper, film, etc., was sensitised with diazoanhydrides and after exposure to light was developed by coupling with phenols or amines. The irradiated anhydride is non-reactive and a positive original thus gives rise to a positive azo-dyestuff copy. The paper is very sensitive and retains its activity a long time. In a later modification the diazo and azo-dyestuff components are coated together on the paper with the addition of tartaric acid, which prevents coupling. After exposure the paper is developed with dry gaseous ammonia. A suitable diazo-compound is, for example, diazotised 1 : 2 : 4-aminonaphthol sulphonic acid, resorcinol being employed as azo-component. The process is known as diazotype printing.

Hydrazines

Aromatic hydrazines are classified in the same manner as the aliphatic compounds (see p. 173). Symmetrical disubstituted aromatic hydrazines, usually termed hydrazo-compounds, have already been dealt with on p. 400.

The *monosubstituted hydrazines*, of which phenyl-hydrazine, $C_6H_5.NH.NH_2$, is the best known example, are the most important. These are generally prepared by the reduction of the corresponding diazonium salts, which may be effected in two ways :—

(*a*) By treating diazonium salts with the calculated amount of stannous chloride in hydrochloric acid solution.

$$C_6H_5.N_2.Cl+4H = \underset{\text{Phenyl-hydrazine hydrochloride.}}{C_6H_5NH.NH_2,\ HCl}$$

(*b*) According to the older method of Emil Fischer, by which phenyl-hydrazine was first discovered. The solution of a diazonium salt is allowed to react with neutral sodium sulphite, whereby a diazo-sulphonate (see p. 406) is formed, *e.g.*,

$$C_6H_5.N_2.Cl+Na_2SO_3 = \underset{\text{Sodium diazobenzene-sulphonate.}}{C_6H_5.N:N.SO_3Na}+NaCl$$

On reduction with sulphurous acid, or zinc dust and acetic acid, the diazo-sulphonate is converted into a hydrazine-sulphonate,

$$C_6H_5N:NSO_3Na+2H = \underset{\text{Sodium phenyl-hydrazine-sulphonate.}}{C_6H_5.NH.NH.SO_3Na}$$

When this is heated with hydrochloric acid the sulphonic group is removed and phenyl-hydrazine hydrochloride obtained.

$$C_6H_5.NH.NH.SO_3Na+H_2O+HCl = C_6H_5.NH.NH_2,\ HCl+NaHSO_4$$

In each of the above methods an amine forms the starting-point, and it is converted into the diazonium salt, and finally into the hydrazine, without actually isolating any of the intermediate products.

The monosubstituted hydrazines are monacid bases, which distil

[1] Kogel, D.R.P., 376385; 386433. See also Ruff and Stein, *Ber.*, 1901, **34**, 1668. D. A. Spencer, *Photographic Journal*, 1928, **68**, 490. Ozalidpapier, and Ozaphanfilm (Kalle & Co., Germany) are prepared by this process.

without decomposition under diminished pressure. They are sparingly soluble in water, readily soluble in alcohol and ether, and reduce Fehling's solution.

Phenyl-hydrazine, $C_6H_5.NH.NH_2$, is prepared on the large scale according to method (*b*) described above. It is a colourless liquid which boils with slight decomposition at 241°, under atmospheric pressure. On cooling it solidifies to large colourless prisms, m.p. 19·6°. The hydrochloride crystallises in white leaflets, which are not very soluble in cold water, and dissolve very sparingly in concentrated hydrochloric acid.

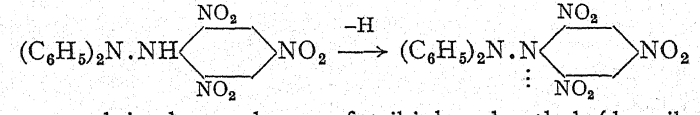
As has already been mentioned, phenyl-hydrazine is a valuable reagent for aldehydes and ketones, and has proved of special service in the investigation of the sugars (see pp. 292 *et seq.*). It is a strong reducing agent, and precipitates cuprous oxide from Fehling's solution ; in such reactions the phenyl-hydrazine decomposes into benzene, nitrogen and hydrogen.

$$C_6H_5.NH.NH_2 = C_6H_6+N_2+2H$$

When treated with energetic reducing agents it yields aniline and ammonia, $C_6H_5.NH.NH_2+2H=C_6H_5.NH_2+NH_3$. Phenyl-hydrazine unites with β-diketones and β-ketonic esters to form derivatives of pyrazole and pyrazolone respectively. Acetoacetic ester, for example, gives phenyl-methyl-pyrazolone, which on methylation is converted into antipyrine, a substance extensively used in medicine as a febrifuge. Owing to its use in the preparation of *antipyrine*, phenyl-hydrazine is produced in large quantities industrially.

The behaviour of **tetraphenyl hydrazine** in dissociating in solution into *nitrogen diphenyl* has already been discussed on p. 398. Hexaphenyl ethane decomposes in a similar manner to form triphenyl methyl (p. 520).

Reference has also been made to the dissociation of **hexaphenyl-tetrazane** into two molecules of *triphenyl-hydrazyl* (p. 399). In the solid state hexaphenyl-tetrazane is colourless ; in solution at 0° it is deep blue, although the blue triphenyl-hydrazyl is extremely unstable. A more stable divalent nitrogen derivative may be obtained from *αα-diphenyl-β-trinitrophenyl hydrazine*, a yellowish-red crystalline substance, which when oxidised in benzene or chloroform solution with lead dioxide yields the monomolecular *αα-diphenyl-β-trinitrophenyl hydrazyl.* The latter forms violet black crystals, soluble in organic solvents to give deep violet solutions. In the above reaction the hydrazine is converted into the completely monomolecular hydrazyl.



This compound is the analogue of tribiphenylmethyl (described later) and is distinguished from other derivatives of divalent nitrogen by its great stability.[1]

[1] S. Goldschmidt and Renn, *Ber.*, 1922, **55**, 628.

VI.—AZO-DYES

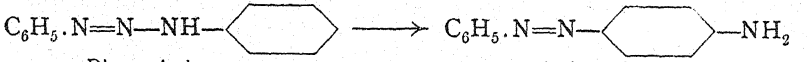
General Methods of Formation

It has already been remarked (see p. 405) that diazo-compounds "couple" with amines and phenols with great readiness to form azo-dyes. Although this process has been formulated in the following pages as a simple change, it is in all probability one of some complexity.[1]

(*a*) Equimolecular quantities of diazonium salts and *primary* or *secondary* aromatic amines react together to form *diazoamino-compounds*,[2] e.g.

$$C_6H_5N_2Cl + H_2N.C_6H_5 = C_6H_5.N:N.NHC_6H_5 + HCl$$
Diazoaminobenzene.

The most interesting property of these compounds is their transformation into the structurally isomeric **aminoazo-compounds.** In the case of diazoaminobenzene this change can be effected by merely allowing the substance to stand in alcoholic solution, and may be catalytically accelerated by the addition of a small amount of aniline hydrochloride.[3]



Diazoaminobenzene Aminoazobenzene.

The isomerisation only takes place readily when the *p*-position to the amino-group is free. If this is already occupied by a substituent the change occurs less easily, and the amino-group then enters the *o*-position to the azo-group. Diazoamino-*p*-toluene, for example, yields *o*-aminoazotoluene.

Aminoazobenzene is the parent substance of a large number of azo-dyes.

(*b*) Diazonium salts and *tertiary* aromatic amines react directly with each other to form aminoazo-compounds.

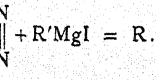
$$C_6H_5.N_2.Cl + HC_6H_4.N(CH_3)_2 = C_6H_5.N:N.C_6H_4.N(CH_3)_2 + HCl$$
Dimethylamino-azobenzene.

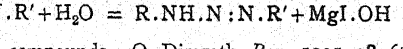
(*c*) In a similar manner phenols unite with diazonium salts in the presence of alkalis to form hydroxyazo-compounds :

$$C_6H_5.N_2.Cl + HC_6H_4(OH) = C_6H_5.N:N.C_6H_4.OH + HCl$$
Phenol Hydroxy-azobenzene.

Here also it has been found that only those hydrogen atoms in the *o*- or *p*-positions to the phenolic hydroxy-group are capable of entering

[1] See Chattaway and H. R. Hill, *J. C. S.*, 1922, **121**, 2756. [2] Diazoamino-compounds are also formed by the action of organomagnesium halides on alkyl and aryl derivatives of hydrazoic acid. Intermediate products containing magnesium are first formed, which on





treatment with water yield diazoamino-compounds. O. Dimroth, *Ber.*, 1905, **38**, 670. [3] For a discussion of this change see H. V. Kidd, *J. Org. Chem.*, 1938, **2**, 198.

into reaction. If hydrogen is only available in the *m*-position, no coupling takes place unless the substituents in the reactive positions are particularly easily detached.[1]

The instances already quoted are simple examples of the typical reactions by which the great majority of the monoazo-dyes are prepared. It is readily understood that these reactions are influenced by the specific constitution of both reagents, and that the velocity of coupling depends on the structure of the amines and phenols, as well as on that of the diazo-compound employed. The introduction of alkyl groups into the benzene ring increases this velocity, but halogen atoms have the reverse effect; thus the trimethyl derivatives, $(CH_3)_3C_6H_2.N_2X$, react very rapidly, and the tribromo-compounds, $Br_3C_6H_2.N_2X$, very slowly. The great influence exerted by the configuration of the diazo-group has already been emphasised (p. 405), the speed of reaction of syndiazo-compounds being always greater than that of the anti-compounds. This fact is of great value in determining the structure of stereoisomerides of this type.

Disruption of Azo-dyes

A point of importance in connection with the structure of the azo-dyes is the behaviour of these compounds towards powerful reducing agents, such as tin and hydrochloric acid. Under this treatment the molecule is disrupted at the double bond —N=N—, so that the amine from which the azo-dye was prepared by diazotisation is regenerated, and the second component with which the diazonium salt was originally coupled is obtained in the form of its amino-derivative. For example, hydroxy-azobenzene, from diazotised aniline and phenol, yields aniline and *p*-aminophenol on reduction:

$$\underset{\text{Hydroxy-azobenzene}}{C_6H_5.N:N.C_6H_4.OH} + 4H = \underset{\text{Aniline}}{C_6H_5.NH_2} + \underset{\text{p-Aminophenol.}}{H_2N.C_6H_4.OH}$$

Hence it may be deduced that in the formation of the azo-dye the coupling occurred in the *p*-position to the phenolic —OH group.

The azo-dye may also be decomposed by treatment with strong nitric acid, which leads in general to the production of the original diazonium salt and a nitro derivative of the original coupling component,[2] *e.g.*

$$\underset{\text{p'-Nitro-p''-methoxy-azobenzene}}{O_2N.C_6H_4.N:N.C_6H_4.OCH_3} + 3HNO_3 = \underset{\substack{\text{p-Nitrobenzene diazonium}\\ \text{nitrate}}}{O_2N.C_6H_4.N_2.NO_3} + \underset{\text{2 : 4-Dinitro-anisole.}}{(O_2N)_2.C_6H_3.OCH_3} + 2H_2O$$

Azo-compounds as Dyes; Technical Preparation and Description of Individual Dyes

The divalent azo-group —N : N— is the *chromophore* of the azo-dyes. When this group is introduced into a hydrocarbon molecule a coloured substance is obtained which is not a dye. Only after the further entry of

[1] Even the *o*- and *p*-hydrogen atoms cannot always be replaced by azo-groups, *cf.* Borsche and Streitberger, *Ber.*, 1904, **37**, 4116. [2] O. Schmidt, *Ber.*, 1905, **38**, 3201.

an *auxochrome* group, such as —OH or —NH_2, capable of conferring acidic or basic character on the compound, does it acquire the property of affixing itself to threads and fibres and thus of functioning as a dye (see p. 72).

The simplest azo-dyes, like those of other types, dye a yellow colour. By increasing the number of auxochrome groups present, or by raising the proportion of carbon in the molecule, the shade gradually deepens, passing through red to violet and blue, or in some cases to brown. In particular, the introduction of naphthalene residues changes the colour to red, violet, blue, and finally to black. Those aminoazo- and hydroxyazo-compounds in which no sulphonic group is present are generally insoluble or only sparingly soluble in water. To be useful, however, a dye of this type must be soluble in water, and since the alkali salts of the sulphonic acid derivatives are more readily soluble than the unsulphonated parent dye-stuffs, the azo-compounds employed technically are for the most part sulphonic derivatives. Azo-dyes are therefore usually prepared directly from sulphonic acids, or the dye may be subsequently sulphonated by treatment with strong sulphuric acid.

Monoazo-dyes directly colour threads of animal origin, such as wool and silk, whereas they only dye cotton indirectly, with the aid of mordants.

Dyeing [1]

The dyeing of spun threads may be mechanical or chemical. In the former case, which does not further concern us, a coloured precipitate (pigment) is produced on the threads, or the latter are coated with a thin layer of a coloured substance. Of much greater interest is chemical dyeing, in which the fabric is usually immersed in a hot aqueous solution of the dye, removing the latter from the solution and becoming thereby coloured. No satisfactory explanation can at present be advanced which will cover all the different processes of chemical dyeing. The majority of chemists assume that in many cases, at all events, dyeing is dependent on a kind of salt formation between the dye and the constituents of the thread, an assumption supported by the fact that a dye always possesses basic or acidic character. Probably the dye is bound to the fibre by the amino-, carboxyl and acid amide groups present in the surface of the threads. It must be emphasised that a characteristic difference is shown between yarns of animal (wool, silk) and those of vegetable origin (cotton, artificial silk). Most dyes colour the former directly (**substantive** or **direct dyeing**) but are not capable of dyeing vegetable threads without special treatment. It is, however, possible to fix the colour to the latter if the fabric is previously impregnated with certain substances which will unite with the dye (**adjective dyeing**). Substances of this type are termed **mordants.** In working with basic dyes, mordants such as tannin are

[1] See *The Synthetic Dyestuffs*, by J. C. Cain and J. F. Thorpe, (Griffin); *Dye Chemistry*, by Fierz-David (Churchill, English edition by F. A. Mason); *Synthetic Colouring Matters*, *Vat Colours*, J. F. Thorpe and C. K. Ingold (Longmans).

employed, which combine with the dye to form insoluble salts, *e.g.* of tannic acid. In most cases the process is completed by treatment with a solution of potassium antimonyl tartrate. With acid dye-stuffs, on the other hand, cotton requires to be impregnated with a basic mordant such as aluminium, iron or chromium hydroxides. The fabric is steeped in an aqueous solution of the metallic acetate and then heated in steam, whereby the acetate is decomposed with the production of the corresponding hydroxide. Acid dyes combine with these hydroxides to form insoluble **lakes.** As will be seen later, alizarin dyes are commonly employed in this manner. Dye-stuffs are also known which are capable of colouring cotton directly or substantively, *i.e.* without the addition of mordants, in the same way as the wool dyes affix themselves to wool. Chief among this class are azo-dyes obtained from benzidine, $NH_2.C_6H_4.C_6H_4.NH_2$, and its derivatives, which contain two of the chromophore groups —N : N—. These are distinguished from monoazo-dyes by the term **disazo-** or **tetrazo-dyes.**

The technical preparation of azo-dyes is generally a comparatively simple operation. In order to obtain hydroxyazo-dyes by the combination of diazo-compounds with phenols, a solution of a diazonium salt is first prepared by treating an aqueous solution or suspension of the required amine, or its sulphonic acid salt, with the requisite amounts of hydrochloric acid and sodium nitrite. After diazotisation is completed, the liquid is allowed to run into an alkaline solution of the desired phenol, or better still, of its sulphonic acid salt, care being taken that the mixture remains alkaline throughout the reaction. The resulting azo-dye is thrown out of solution by the addition of common salt, filtered in a filter press, and dried. Combination between diazonium salts and amines, which leads to the formation of aminoazo-dyes, is effected directly in neutral aqueous solution, or in many cases by adding an alcoholic solution of the amine to a concentrated aqueous solution of the diazo-compound.

A detailed description of the azo-dyes is not possible in a general text-book such as this. The following examples are selected from the very large and ever-increasing number of these compounds known, of which only those of good colour and fastness to light are used in industry.

Dimethylamino-azobenzene sulphonic acid,[1] $SO_2.C_6H_4.NH.N=C_6H_4=N(CH_3)_2$, is produced by the action of dimethylaniline on a diazotised solution of sodium sulphanilate. The sodium salt of the compound dyes wool and silk an orange colour, and has been employed for this purpose under the name of **helianthine** or **methyl orange.** It is largely used as an indicator in volumetric analysis, the yellow colour of the aqueous solution changing to red on acidification.

Chrysoidine, *diamino-azobenzene,*

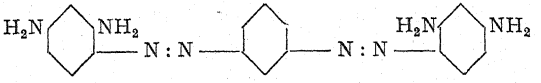
$$C_6H_5.N:N.C_6H_3(NH_2)(NH_2)$$

is prepared by mixing equivalent solutions of benzene diazonium chloride and

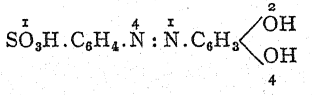
[1] The numbers attached to this and the following formulæ indicate the position of the substituents in the benzene nucleus. In the above case the free acid possesses a quinonoid structure, Hantzsch, *Ber.*, 1908, 41, 2435. Fox, *Ber.*, 1908, 41, 1989.

m-phenylene diamine. Its hydrochloride is comparatively soluble in water and is used in dyeing wool, particularly for pale shades. Wool mordanted with tannin is coloured orange yellow.

Bismarck brown may be prepared by the action of nitrous acid on *m*-phenylene diamine. It resembles chrysoidine in its properties, and is employed for dyeing wool and leather goods. Bismarck brown is a mixture, the chief constituent being the hydrochloride of the following diazo-compound.

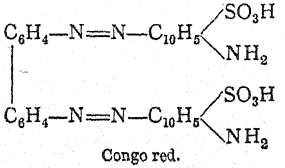


Tropaeoline O, *dihydroxy-azobenzene*-p-*sulphonic acid,*



is obtained by pouring a diazotised solution of sulphanilic acid into an alkaline solution of resorcinol, or by coupling benzene diazonium chloride with resorcinol and subsequently treating the product with sulphuric acid. In acid solution it colours wool and silk golden yellow, and is used more particularly in the silk industry.

Among the substantive azo-dyes, which, as already mentioned, are able to dye cotton directly without the aid of mordants, are included certain compounds obtained by diazotising *p*-diamines and combining the bis-diazonium salts thus formed with amines and phenols, particularly with naphthols and naphthol sulphonic acids. For example, when benzidine is diazotised and coupled with α-naphthionic acid, it yields **Congo red,** which is much used in dyeing.



Congo red.

VI

Aromatic Sulphonic Acids

Formation.—When aromatic hydrocarbons or their derivatives are treated with sulphuric acid they yield sulphonic acids, in which hydrogen of the benzene nucleus is replaced by the sulphonic group SO_3H, *e.g.* $C_6H_6+H_2SO_4 = C_6H_5.SO_3H+H_2O$. *Sulphonation* is effected by the use of ordinary sulphuric acid,[1] or of fuming acid containing varying proportions of anhydride, the temperature being regulated according to the ease with which the reaction occurs. In this way, by choosing the conditions, it is possible to prepare mono- or polysulphonic acids. In the case of benzene a maximum of three sulphonic groups may thus be introduced into the molecule.[2] The sulphonic acids either separate directly

[1] A. Guyot, *C.*, 1920, I, 565. [2] R. Behrend and Mortelsmann, *Ann.*, 1911, **378**, 352.

from the acid mixture on cooling, or are precipitated in the form of their alkali salts by the addition of salt, sodium acetate or potassium chloride. They may also be separated from the excess of sulphuric acid as the soluble calcium, barium or lead salts.

Properties and Chemical Behaviour.—The sulphonic derivatives of the hydrocarbons are all readily soluble in water, and form more or less easily crystallisable substances of strongly acidic character. By the action of superheated steam, or of concentrated hydrochloric acid at 150°, they may be converted into the original hydrocarbons (see p. 379). When fused with alkalis they yield phenols, a reaction which is of great importance technically.

$$C_6H_5.SO_3K + KOH = C_6H_5.OH + K_2SO_3$$

On being heated with potassium cyanide the salts of sulphonic acids pass into the corresponding nitriles, which may be hydrolysed to carboxylic acids.

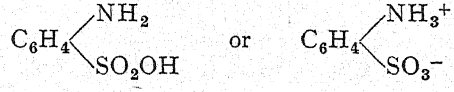
$$\underset{\text{Potassium benzene sulphonate}}{C_6H_5.SO_3K} \xrightarrow{KCN} \underset{\text{Benzonitrile}}{C_6H_5.CN} \longrightarrow \underset{\text{Benzoic acid.}}{C_6H_5.COOH}$$

The alkali salts of the sulphonic acids, on being treated with phosphorus pentachloride, yield *sulphonic chlorides* of the formula $R.SO_2.Cl$. With ammonia or ammonium carbonate, these give crystalline *sulphonamides*, $R.SO_2.NH_2$. The latter are frequently used in the identification of the sulphonic acids. The *anhydrides* are colourless neutral substances, which generally crystallise well and are remarkably stable towards water or weak alkalis.[1]

Benzene sulphonic acid, $C_6H_5.SO_3H$, crystallises in plates, m.p. 66°, which very readily dissolve in water. Its chloride may be used for distinguishing between primary and secondary amines (p. 172).—**Benzene disulphonic acids.** $C_6H_4(SO_3H)_2$. When benzene is heated with fuming sulphuric acid, a mixture of the *m*-disulphonic acid, m.p. 63°, with a little *p*-compound, m.p. 132°, is formed. The sulphonation of toluene leads mainly to the formation of **o-** and **p-toluene sulphonic acids.**

The nitration of benzene sulphonic acid or the sulphonation of nitrobenzene yields in each case a mixture of *o-*, *m-* and *p-nitrobenzene sulphonic acids*, containing a preponderance of the *m*-compound. On reduction these yield the three *aminosulphonic acids*, which are colourless crystalline compounds having acidic, but no basic, properties. The sulphonic acids derived from primary amines may be diazotised and are of value in the preparation of azo-dyes (p. 412).

Sulphanilic acid, p-*aminobenzene sulphonic acid*,



is obtained by heating aniline to 180° with fuming sulphuric acid containing 8 to 10 per cent. of anhydride. It is only sparingly soluble in cold water, and crystallises in rhombic plates ($+2H_2O$). It yields quinone

[1] H. Meyer and Schlegel, *Monats.*, 1913, **34**, 561.

on oxidation with chromic acid, and is an important starting material in the preparation of azo-dyes.

Sulphanilamide, $H_2N.C_6H_4.SO_2NH_2$, the amide of sulphanilic acid, is a valuable remedy for the treatment of streptococcal infections (see p. 850).

Metanilic acid, or m-*aminobenzene sulphonic acid*, is also used in the manufacture of dyes and is obtained from *m*-nitrobenzene sulphonic acid by reduction with iron and hydrochloric acid.

Phenol sulphonic acids, sulphobenzoic acids, and other more complex sulphonic derivatives are dealt with in later chapters.

Sulphinic acids, $R.SO_2H$, may be prepared by reducing arylsulphonic chlorides with zinc dust and water. They are crystalline compounds

$$C_6H_5.SO_2Cl \longrightarrow C_6H_5.SO_2H$$

which dissolve sparingly in cold water.

VII

Aromatic Arsenic Compounds[1]

Mainly in consequence of the researches of P. Ehrlich, organic compounds of arsenic have been extensively employed in medicine. Only a few of the more important of these will be treated here.

Primary Aromatic Arsonic (Arsinic) Acids

Preparation.—It was shown by Ehrlich and Bertheim that the arsenic compound discovered in 1863 by Béchamps, by heating aniline arsenate, and employed in medicine under the name of **atoxyl**, was not, as Béchamps assumed, an anilide of arsenic acid, but *p*-amino-phenylarsonic acid.

In general, when primary aromatic amines are fused with arsenic acid, the arsenic group takes up the para-position with respect to nitrogen, with the formation of *p*-aminoaryl arsonic acids. If the *p*-position is already occupied, then either no substitution occurs or the corresponding *o*-amino-derivative is obtained :

$$NH_2.C_6H_5 + AsO_4H_3 = NH_2.C_6H_4.AsO_3H_2 + H_2O$$

Many other aromatic compounds, such as phenols and certain indoles, behave in the same manner.

This process is an exact parallel to the production of sulphanilic acid by the action of heat on aniline sulphate (p. 417), and may therefore be described as **arsenation** (*cf.* sulphonation) and the reaction products as **arsanilic acids.** Most of the aminoaryl arsonic acids known have been prepared in this way.

[1] See *Organic Compounds of Arsenic and Antimony*, by G. T. Morgan (Longmans, Green & Co., 1918). *Organische Arsenverbindungen und ihre chemotherapeutische Bedeutung*, by Nierenstein (Enke, Stuttgart, 1912). *Handbuch der organischen Arsenverbindungen*, by A. Bertheim (Enke, 1913). L. F. Hewitt, H. King and W. O. Murch, *J. C. S.*, 1926, 1355.

Among other syntheses of aromatic arsenic derivatives the following may be mentioned. On treating diazo-compounds with arsenious acid or its salts the diazo-group is replaced by arsenic to give primary arsonic acids.[1]

$$RN{:}NX + As(OH)_3 = R.AsO(OH)_2 + N_2 + HX$$

This reaction may also be used to prepare the corresponding antimony derivatives. Acids containing both these metals are obtained by the interaction of antimony oxide with diazotised amino-phenylarsonic acids (or of arsenites with diazotised aminophenyl-antimonic acids); in this manner phenylene-arsonic-antimonic acids are formed [2] $(C_6H_4.AsO_2.SbO_2.nH_2O)_x$.

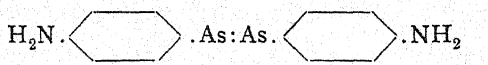
Properties.—Aromatic amino-arsonic acids are very reactive and may be used in a variety of syntheses. In particular they are readily diazotised, and the diazoaryl arsonic acids so obtained undergo the usual decompositions of diazo-compounds (see p. 403), and couple in the normal manner to give azo-dyes, all of which are soluble in alkalis owing to the presence of the arsonic acid residue, AsO_3H_2. In its properties this group shows a general resemblance to the sulphonic group, SO_3H, and in some reactions to the carboxyl group, CO_2H.

***p*-Aminophenylarsonic acid, Arsanilic acid,** $H_2N.C_6H_4.AsO_3H_2$, is the most important of these acids, and, as already described, is obtained by the arsenation of aniline. It crystallises in colourless needles, and is difficultly soluble in cold water; in hot water it dissolves easily to give an acid solution. As an acid the compound is readily soluble in alkalis, but it also possesses basic properties, as shown by its solubility in an excess of dilute mineral acid. It does not melt at any particular temperature, but decomposes in the neighbourhood of 300°. The sodium salt was formerly employed in medicine under the name of **atoxyl** in cases of syphilis and sleeping sickness. In the year 1902, when this substance was first placed on the market, experiments were being carried out by Ehrlich and Shiga with the object of curing parasitic diseases by the injection of suitable chemical compounds. In this work the action of atoxyl on trypanosomes was investigated, with results which led to further experiments with arsenic derivatives and to the valuable discovery of salvarsan.

Reduction Products of Arsanilic Acids.

pp′-Diamino-arsenobenzene [3]

On energetic reduction the arylarsonic acids are converted into arseno-compounds, that produced from *p*-aminophenyl arsonic acid (arsanilic acid) being *pp′*-diamino-arsenobenzene or *p*-arsenoaniline, possessing the structure

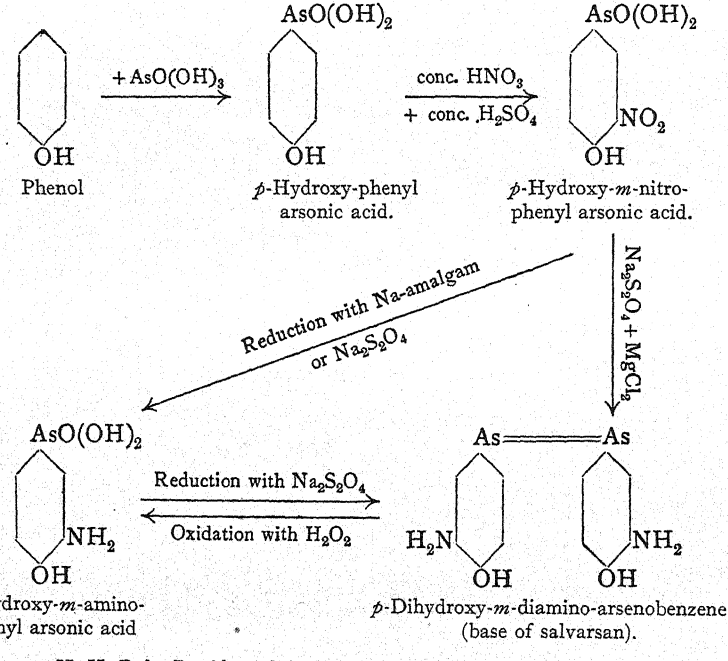


[1] H. Bart, D.R.P. 250264. *Ann.*, 1922, **429**, 55. E. Sakellarios, *Ber.*, 1924, **57**, 1514. E. Maschmann, *Ber.*, 1924, **57**, 1759. [2] Hans Schmidt, *Ber.*, 1924, **57**, 1124. [3] P. Ehrlich and Bertheim, *Ber.*, 1911, **44**, 1260.

This compound can be prepared in a variety of ways, such as by the reduction of *p*-aminophenyl arsonic acid with sodium hydrosulphite, or with stannous chloride and hydriodic acid. It melts at 260°, is insoluble in water and aqueous alkalis, but as a base is readily soluble in dilute hydrochloric acid. Oxidising agents attack it rapidly, as the arseno-compounds in general are characterised by strong reducing properties. Diamino-arsenobenzene also gives the reactions of primary amines. It is readily diazotised, converted into azo-dyes, and condensed with aldehydes.

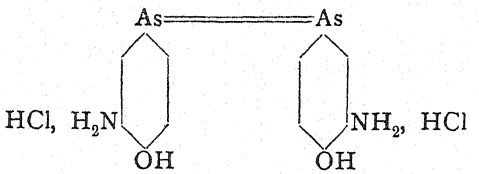
The reduction of *p*-aminophenyl arsonic acid to diamino-arseno-benzene is found to bring about a great increase in toxic power and also in trypanocidal action, in explanation of which it has been suggested that the chemoceptors of the parasites are able to attach themselves to the trivalent but not to the pentavalent arsenic residue.[1] The belief that only those radicals containing trivalent arsenic exert a direct trypanocidal action led to the examination of other arsenic compounds and to the isolation of salvarsan.

***p*-Dihydroxy-*m*-diamino-arsenobenzene (Base of Salvarsan).**—This compound, the hydrochloride of which, under the name of salvarsan or arsphenamine excited such general interest in the medical world, was prepared from *p*-hydroxy-phenyl-arsonic acid. The latter was obtained directly from phenol and arsenic acid, in the same manner as phenol-sulphonic acid is obtained from phenol and sulphuric acid. It was then nitrated, and the resulting *p*-hydroxy-*m*-nitrophenyl arsonic acid reduced as indicated in the following scheme :



[1] See, however, H. H. Dale, Presidential Address to Section I. (Physiology), *B. A. Rep.*, 1924.

Dihydrochloride of *p*-dihydroxy-*m*-diamino-arsenobenzene, Salvarsan or "606" [1]



In the preparation of the dihydrochloride the crude base obtained by the above process is dissolved in methyl alcohol containing the theoretical proportion of hydrochloric acid, and the mixture stirred with several times its volume of well-cooled ether. All these and the following operations are, as far as possible, conducted in the absence of air. The hydrochloride separates out as a microcrystalline precipitate and is filtered off under suction, washed with ether, and dried *in vacuo* over sulphuric acid and paraffin wax. After this it is immediately sealed up in small tubes which are either evacuated to a high degree or filled with an indifferent gas.

Salvarsan is a yellow, crystalline powder, readily soluble in water, methyl alcohol and glycerol, less readily soluble in ethyl alcohol and insoluble in ether. A point requiring careful attention in its practical use is that, like other arseno-compounds, it is readily oxidised. When exposed to the air it rapidly acquires a proportion of the far more poisonous *amino-hydroxy-phenylarsine oxide*.[2] As an injection of such a preparation would be dangerous for the patient, salvarsan is preserved in evacuated tubes, or in ampoules which have first been exhausted and then filled with an indifferent gas.

Salvarsan has proved a valuable specific for certain dangerous protozoal diseases, particularly syphilis, and has also been used with success in cases of *malaria tertiana*.

Neosalvarsan. — Dihydroxy-diamino-arsenobenzene, the base of salvarsan, condenses with sodium formaldehyde sulphoxylate, $HO.CH_2.SO_2Na$, when one or two of the sulphoxylate groups may enter the molecule. The sodium salt of the compound containing one such group has been placed on the market under the name of neosalvarsan or neo-arsphenamine. In this product an NH_2 of salvarsan has been converted into $NH.CH_2.SO_2Na$. Neosalvarsan possesses the advantage that when dissolved in water or physiological salt solution it is suitable for injection without further preparation. Solutions of salvarsan, on the other hand, are acidic, and require to be neutralised with alkali immediately before injection.

Metallic derivatives such as *copper salvarsan* and *silver salvarsan* also possess valuable therapeutic properties.[3]

Tryparsamide.—Attention has recently been directed towards the

[1] Ehrlich and Bertheim, *Ber.*, 1912, 45, 756. [2] Ehrlich and Bertheim, *Ber.*, 1912, 45, 764.
[3] P. Karrer, *Ber.*, 1919, 52, 2319. Binz, Bauer and Hallstein, *Ber.*, 1920, 53, 416.

use of compounds containing arsenic in a higher state of combination. An example of this kind is tryparsamide (sodium N-phenyl glycinamide *p*-arsonate), $H_2N.CO.CH_2.NH.C_6H_4.AsO_3HNa$. This compound, which has only one-twentieth of the toxicity of salvarsan, is used in the treatment of sleeping sickness and syphilis.

VIII

Phenols

Formation.—The phenols are compounds in which hydrogen atoms of the benzene nucleus [1] have been replaced by hydroxyl groups. According to the number of atoms substituted in this manner we speak of mono-, di- or trihydric phenols and so on. The monohydric derivatives, in particular, are formed during the dry distillation of wood and coal. Hence they are present in coal tar, from the carbolic oil of which they are prepared industrially (see p. 423). Phenols may be prepared by the following methods :—

1. By the fusion of sulphonic acids with sodium or potassium hydroxide [2] (p. 417).

2. From diazonium salts by heating with water (see p. 403). The sulphates are best employed for this reaction, since with nitrates the nitric acid set free may lead to the formation of nitrophenols.

3. By the action of oxygen on aromatic organo-magnesium compounds, and decomposition of the resulting product with dilute hydrochloric acid (see p. 136).

Properties and Reactions.—In their structure, as well as in many of their reactions, the phenols resemble the tertiary alcohols of the aliphatic series. Like these they form esters, but show a characteristic distinction in their weakly acidic nature, due to the presence of the aromatic hydrocarbon radical. This property is illustrated by the ease with which phenols dissolve in aqueous alkalis, with the formation of salts. Phenols, however, are only weakly acidic, and their salts, unlike those of the carboxylic acids, are decomposed by carbon dioxide. These facts are frequently utilised in the purification of phenols from neutral or more strongly acidic substances. The acid character of the phenolic hydroxyl group is influenced by the entrance of other substituents into the nucleus, and is strengthened, for example, by the presence of nitro-groups.

The hydrogen atom of the hydroxyl group may also be replaced by hydrocarbon radicals, with the formation of ethers. These are prepared

[1] If the hydroxyl group enters into a side chain instead of the nucleus, an aromatic alcohol is formed (*e.g.* benzyl alcohol, $C_6H_5.CH_2OH$). Compounds of this type are treated later.

[2] It should be remembered that, in the absence of other substituents, the monohalogen derivatives of benzene do not exchange halogen for hydroxyl when treated with alkali hydroxides, thus differing from the alkyl halides.

from metallic phenates by interaction with alkyl halides or salts of alkyl sulphuric acids.

$$C_6H_5ONa + IC_2H_5 = C_6H_5.OC_2H_5 + NaI$$

If the vapour of a phenol, alone or mixed with that of benzene, is led over thoria at 390° to 450°, the corresponding ether is produced, *e.g.* $C_6H_5.O.C_6H_5$, from phenol itself. Mixed ethers, such as $C_6H_5.O.CH_3$, are obtained in the same manner from the mixed vapours of a phenol and an alcohol.[1] Phenols are also quite easily phenylated by treating their alkali salts with phenyl bromide in the presence of copper as catalyst.

By the action of phosphorus pentachloride the hydroxyl group of a phenol can be replaced by chlorine, though less readily than in the case of the alcohols. When heated with zinc dust, phenols are converted into the parent hydrocarbons. The fact that the hydrogen atoms attached to the nucleus of a phenol are more easily substituted than those in the aromatic hydrocarbons has already been emphasised (see p. 368). Most of the phenols give characteristic colour reactions with ferric chloride in aqueous solution.

Certain other reactions which are peculiar to polyhydric phenols are described later.

A large industry has arisen out of the discovery by Baekeland that **synthetic resins** or **bakelites** can be prepared by condensing formaldehyde with phenols such as phenol and cresol. Such resins are readily coloured and moulded, and are employed in ever-increasing quantities for electrical insulators and the manufacture of a variety of articles. A further description of these products is given later (see synthetic resins).

1. Monohydric Phenols and their Derivatives

Phenol, *carbolic acid, Acidum carbolicum,* C_6H_5OH, is the chief constituent of that fraction of coal tar boiling at 170° to 230°, and generally known as middle or carbolic oil. It is prepared from this source, after removal of naphthalene, by shaking out with dilute caustic soda. The aqueous layer is run off and phenol precipitated with sulphuric acid or carbon dioxide. Finally it is purified by distillation.

The formation of phenol from aniline and other sources has been indicated above.

In the pure form phenol is a white crystalline substance, m.p. 43°, which gradually turns pink on keeping. It is liquefied on addition of a very small proportion of water, and dissolves completely in 15 parts at 20°. It possesses a peculiar pungent smell, is poisonous, and is employed in aqueous solution (*e.g.* 3 per cent.) as a disinfectant.

When treated with bromine it yields a white precipitate of 2 : 4 : 6-*tribromophenol*, a reaction which is used for its separation and quantitative estimation. Phenol dissolves readily in alkali hydroxides with the formation of sodium and potassium phenates, these being obtained in the solid

[1] Sabatier and Mailhe, *C. r.*, 1910, **151**, 359, 492.

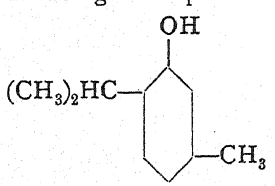
state when the solutions are evaporated. Under special conditions carbon dioxide interacts with sodium phenate to give as final product sodium salicylate (see Salicylic Acid). This reaction is used in the commercial preparation of *salicylic acid*. Phenol is used in large quantities for the production of bakelite resins, to which reference has been made above.

HOMOLOGUES, ESTERS AND ETHERS OF PHENOL

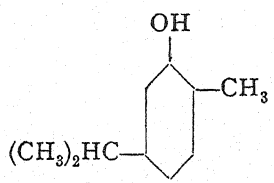
The **cresols**, $CH_3.C_6H_4.OH$, may be regarded as methyl derivatives of phenol or as hydroxy derivatives of toluene; they are found with phenol in coal tar. The isomers are not usually isolated from this source in the pure state, but are placed on the market in the crude condition. Since they are cheaper than phenol, they are much used as disinfectants.[1]

The crude cresols are rendered soluble in water by the addition of resin soap or oil soap. Preparations of this kind sold as disinfectants are **cresoline** and **lysol**. The individual cresols are prepared by the methods quoted on p. 422. **o-Cresol** melts at 30° and boils at 191°; **m-cresol** melts at 4° and boils at 203°. **p-Cresol** (m.p. 36°, b.p. 202°) is found among the putrefaction products of egg albumin.

Other homologues of phenol are *thymol* and *carvacrol*.



Thymol
(3-Methyl-6-isopropyl-phenol)



Carvacrol
(2-Methyl-5-isopropyl-phenol).

Thymol occurs together with cymene, $C_{10}H_{14}$, and thymene, $C_{10}H_{16}$, in oil of thyme, from which it is isolated by treating the oil with caustic soda and precipitating the solution with hydrochloric acid. It forms large crystals, m.p. 44° and b.p. 230°, which smell of thyme. It is used as a mouth-wash and in the treatment of wounds. **Carvacrol**, present in *Origanum hirtum*, is obtained from its isomeride carvone, found in carraway oil, by heating with glacial phosphoric acid, or from camphor by heating with iodine. It melts at 0° and boils at 236°.

Esters of phenols are produced by the action of acid chlorides or anhydrides on phenols or their alkali salts. Like the esters of aliphatic alcohols they are decomposed into their components when heated with alkalis. The sulphuric and glucuronic esters of phenols and of many heterocyclic hydroxy-compounds which are eliminated in the urine play an important part in the animal organism, since by union with acids the phenols lose their poisonous character.

Phenylsulphuric acid, *phenolsulphuric acid*, $C_6H_5.O.SO_3H$, is unknown in the free state. The potassium salt occurs in urine, and may be prepared from potassium phenate

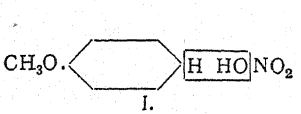
[1] 4-n-*Amyl*-m-*cresol* has been found to combine comparatively low toxicity with a high germicidal value (Coulthard, Marshall and Pyman, *J. C. S.*, 1930, 281).

by heating it with potassium pyrosulphate. When heated in a sealed tube the salt isomerises into potassium *p*-phenolsulphonate, $C_6H_5.O.SO_3K \longrightarrow HO.C_6H_4.SO_3K$. *Phenyl acetate*, $C_6H_5.O.COCH_3$, boils at 195°.

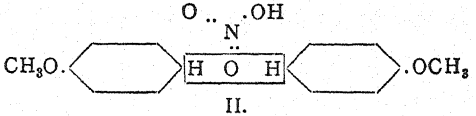
Ethereal derivatives of phenol are obtained in the same manner as from aliphatic compounds, by the action of phenates on alkyl halides or dimethyl sulphate

$$C_6H_5.O.Na+I.CH_3 = C_6H_5.O.CH_3+NaI$$

It has already been stated that aromatic halogen derivatives react less readily than those of the aliphatic series; similarly the purely aromatic ethers, such as $C_6H_5.O.C_6H_5$, can only be prepared by the above reaction in the presence of finely-divided copper as catalyst. Phenolic ethers are exceedingly stable substances. Those containing an aliphatic radical are only decomposed by prolonged heating with alcoholic potash or hydriodic acid, $C_6H_5.OCH_3+HI=C_6H_5.OH+CH_3I$. When treated with nitric acid,[1] two reactions proceed concurrently, viz., nitration of the ether I, and conversion into derivatives of diphenyl nitric acid (diphenyl-hydroxylamine oxide) II:



I.



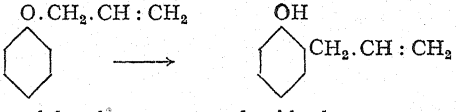
II.

Phenyl methyl ether, **anisole**, $C_6H_5.O.CH_3$, is a colourless liquid, b.p. 155°, which resembles the ethyl ether, **phenetole**, $C_6H_5.O.C_2H_5$, b.p. 172°, in possessing a very characteristic smell. **Phenyl ether**, $C_6H_5.O.C_6H_5$, may be obtained from phenol by the dehydrating action of zinc chloride, $2C_6H_5OH=(C_6H_5)_2O+H_2O$, and also by warming benzene diazonium sulphate with phenol. It is best prepared by heating potassium phenate with bromobenzene in the presence of finely-divided copper:

$$C_6H_5.OK+BrC_6H_5 \longrightarrow C_6H_5.O.C_6H_5+KBr$$

It is a pleasant-smelling substance, m.p. 28° and b.p. 253°, which is not hydrolysed by heating with hydriodic acid.

Phenyl allyl ether has been shown by L. Claisen to undergo rearrangement into *o*-allyl-phenol on being heated at 200°.



The reaction is unaffected by the presence of acids, bases or a solvent and has been shown to be intramolecular.[2]

SULPHONIC, NITRO-[3] AND AMINO-DERIVATIVES OF PHENOL

Ortho- and *para-phenolsulphonic acids*, $HO.C_6H_4.SO_3H$, are formed when phenol dissolves in concentrated sulphuric acid. Under the influence of heat the *o*-compound passes into the *p*-compound. The potassium salt of the *p*-acid is also obtained by the isomerisation of the potassium salt of phenylsulphuric acid (see above). When *p*-phenolsulphonic acid is treated with iodine it yields 2 : 6-*diiodo*-p-*phenolsulphonic* acid, used

[1] K. H. Meyer and Billroth, *Ber.*, 1919, **52**, 1476. [2] See Kincaid and D. S. Tarbell, *J. A. C. S.*, 1939, **61**, 3085; Hurd and Schmerling, *J. A. C. S.* 1937, **59**, 107. [3] The tautomerism observed by Hantzsch (*Ber.*, 1906, **39**, 1073, 1084) in the case of the esters of nitrophenols, and the light thus thrown on the constitution of the nitrophenols themselves, is discussed later in connection with the quinones. *Nitrosophenols* are described under oximes of quinone.

as an antiseptic under the name of *Sozo-iodol.* m-*Phenolsulphonic acid* is formed from *m*-benzene-disulphonic acid by the action of potassium hydroxide.

Phenol is very easily nitrated, and yields, according to conditions, mono-, di- or trinitrophenols, in which the nitro-group substitutes almost entirely in the *o*- and *p*-positions, and little or not at all in the *m*-position to the hydroxyl. Even dilute nitric acid can nitrate phenol. As has already been mentioned, the nitro-derivatives are more strongly acidic than phenol itself, and decompose carbonates.

o-**Nitrophenol**, $HO.C_6H_4.NO_2$, forms yellow crystals, m.p. 45° and b.p. 214°. *p*-**Nitrophenol** forms colourless needles, m.p. 114°. These isomers can be separated by distillation in steam in which only the *o*-compound is volatile, the *p*-nitrophenol remaining behind. *m*-**Nitrophenol** is obtained by the diazotisation of *m*-nitraniline and is a yellow, crystalline substance, m.p. 96°.

Picric acid, 2:4:6-*trinitrophenol*, $HO.C_6H_2(NO_2)_3$, is a compound of great technical importance. It is prepared on the large scale by treating phenol (1 part) with sulphuric acid (4 to 6 parts of sp. gr. 1·84), the mixture being then added with stirring to concentrated nitric acid (7·5 parts of sp. gr. 1·38). During the addition the temperature is maintained at about 10°, after which the mixture is gradually warmed to about 80° to 90°, till gas evolution ceases. Picric acid crystallises out on cooling. It is filtered off or separated in a centrifuge, and recrystallised from hot water. Not more than three nitro-groups can be introduced into phenol by treatment with nitric acid.

Picric acid is also formed by the action of nitric acid on many organic substances, such as silk, wool, Peru balsam and indigo.

Picric acid crystallises in pale yellow leaflets of an intensely bitter taste. It is only sparingly soluble in cold water, and melts at 122°. In an acid bath it dyes silk and wool yellow, but the colour is not very fast.

Although not now used as a dye, picric acid is employed in large quantities as an explosive. When suddenly heated, or detonated by fulminate of mercury, it decomposes according to the equation, $C_6H_2(NO_2)_3OH = 6CO+H+3N+H_2O$. Picric acid is an extremely powerful explosive, and is known by various names, *e.g.* **lyddite** in Great Britain, **melinite** in France. It is used as a filling for shells and as an explosive by sappers. During the last few decades, **trinitrotoluene** (T.N.T.), $C_6H_2(NO_2)_3CH_3$, has come into use as a filling for high explosive shells. While this compound is almost as powerful an explosive as picric acid, it is greatly superior to it in a number of other respects.

Characteristic among the chemical properties of picric acid are those due to its strongly acidic nature. When treated with phosphorus pentachloride, picric acid exchanges the hydroxyl group for chlorine and yields **picryl chloride**, $C_6H_2(NO_2)_3.Cl$, m.p. 83°, which resembles the acid chlorides in its behaviour. With ammonia this compound is converted

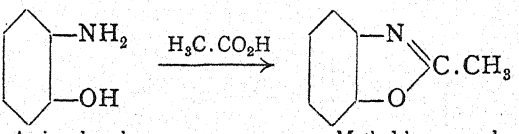
into **picramide**, $C_6H_2(NO_2)_3NH_2$, m.p. 188°. Potassium picrate, $C_6H_2(NO_2)_3OK$, and *ammonium picrate*, $C_6H_2(NO_2)_3ONH_4$, are as explosive as the free acid, although little use is made of them. When the silver salt is treated with ethyl bromide it yields *trinitrophenetole*, $(NO_2)_3C_6H_2.OC_2H_5$, together with *aci*-trinitro-phenol ethyl ether,[1]

$$(NO_2)_2C_6H_2\begin{matrix}=O\\ \diagdown NO.OC_2H_5\end{matrix}.$$

Picric acid unites with many aromatic hydrocarbons, such as naphthalene and anthracene, to form beautifully crystalline coloured addition compounds, which are sometimes of service in the recognition and isolation of these hydrocarbons.

On reduction the nitrophenols give aminophenols, in the same way as nitro-hydrocarbons yield amino-compounds. Aminophenols, as would be expected, are both acids and bases. In the free state they readily undergo decomposition, but the hydrochlorides are more stable.

o-*Aminophenol*, $NH_2.C_6H_4.OH$, melts at 170°, and its methyl ether, ***o*-anisidine**, $NH_2.C_6H_4.OCH_3$, is a liquid of b.p. 218°. Like the *o*-phenylene diamines, the *o*-aminophenols tend to form cyclic compounds, *e.g.* with carboxylic acids they yield *benzoxazoles*,



o-Aminophenol — *μ*-Methyl-benzoxazole (Ethenyl-aminophenol).

Diethyl-m-*aminophenol*, $(C_2H_5)_2N.C_6H_4.OH$, m.p. 87°, and *dimethyl*-m-*aminophenol*, $(CH_3)_2N.C_6H_4.OH$, are prepared by fusing together diethyl- or dimethylaniline *m*-sulphonic acid and sodium hydroxide. They are used for the manufacture of rhodamine dyes.

***p*-Aminophenol**, m.p. 184°, is formed when *p*-nitrophenol is reduced with iron and hydrochloric acid, and is best prepared by the electrolytic reduction of nitrobenzene in strong sulphuric acid solution (see p. 387). An alkaline solution of *p*-aminophenol, containing a little sodium sulphite, is sold as a photographic developer under the name of **rodinal.** Its methyl derivative, $CH_3.NH.C_6H_4.OH$, known as **metol,** is also used for the same purpose. p-*Phenetidine*, $NH_2.C_6H_4.OC_2H_5$, the ethyl ether of *p*-aminophenol, is employed in the preparation of aceto-*p*-phenetidine or **phenacetine** (*p*-ethoxy-acetanilide), $CH_3CO.NH.C_6H_4.OC_2H_5$, m.p. 135°, which is used as an antipyretic and in cases of neuralgia, and also in the preparation of **lactophenine** or lactyl-phenetidine and a number of other compounds.

2 : 4-*Diaminophenol*, obtained from 2 : 4-dinitrophenol, is also of interest, as its sodium salt is employed as a photographic developer under the name of **amidol.**

[1] Hantzsch and Gorke, *Ber.*, 1906, **39**, 1077.

2. Dihydric Phenols and their Derivatives

In the main the di- and polyhydric phenols closely resemble the monohydric compounds in their properties, but many of them are strong reducing agents in alkaline solution. They are generally prepared from the di- or polysulphonic acids of aromatic hydrocarbons, or from phenol-sulphonic acids, by fusion with potassium hydroxide. According to the relative positions of the two hydroxyl groups the dihydric phenols show characteristic differences in chemical behaviour.

The *ortho*-compounds frequently give green colorations with ferric chloride, and readily yield heterocyclic derivatives in which the two hydrogen atoms of the hydroxyl groups are replaced by a divalent radical.

The *meta*-compounds usually give a deep violet coloration with ferric chloride, and undergo the fluorescein reaction, *i.e.*, when heated with phthalic anhydride they yield *phthaleins*, which show a green fluorescence in alkaline solution.[1]

The *para*-compounds on oxidation very easily pass into quinones, which are readily recognised.

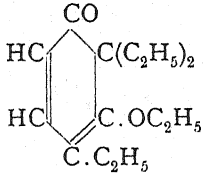
Catechol, *pyrocatechin*, o-*dihydroxy-benzene*, $C_6H_4(OH)_2$, m.p. 104°, occurs in living as well as in fossil plants. Thus it has been obtained from catechin, moringatannic acid, kinotannic acid and other sources containing tannic acids, and has been shown to be present in crude wood tar, crude beet sugar, and the tar waters from bituminous shale and coal. It is formed by oxidising phenol with hydrogen peroxide, and from *o*-benzenedisulphonic acid or *o*-phenolsulphonic acid by fusion with alkali. The monomethyl ether, *guaiacol*, $HO.C_6H_4.OCH_3$, occurs in the crude creosote of beech tar. An aqueous solution of catechol gives a green colour with ferric chloride, which changes to deep red on the addition of alkalis, alkali carbonates or ammonia. The red colour is due to the formation of the complex $[Fe(C_6H_4O_2)_3]H_3$, which in alkaline solution gives a red anion. Other phenols and phenol-carboxylic acids also give deep colorations with ferric chloride in alkaline solution. A physiologically important derivative of catechol is adrenaline (p. 843).

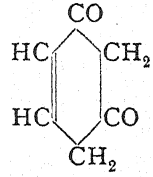
Resorcinol, m-*dihydroxy-benzene*, $C_6H_4(OH)_2$, m.p. 119°, is prepared technically by fusing benzene disulphonic acid with alkali at 235° to 270°. It crystallises in rhombic prisms or plates, which readily dissolve in water, alcohol or ether, and give a deep violet coloration with ferric chloride. It yields fluorescein on being heated with phthalic anhydride, and is used in the preparation of dyes. With cold nitric acid it yields a trinitro-derivative known as *styphnic acid*, m.p. 175°, which is also formed by treating various gum-resins with nitric acid. It has been shown [2] that the action of ethyl iodide and potassium hydroxide on resorcinol leads to the forma-

[1] This reaction is hindered by substitution in the meta-position to the two hydroxyl groups.

[2] Herzig and Zeisel, *Monats.*, 1890, **11**, 291; 1893, **14**, 376. *Ber.*, 1920, **53**, 518; 1921, **54**, 1403.

tion of resorcinol diethyl ether, accompanied by not inconsiderable amounts of tri- and tetraethyl derivatives of resorcinol. The latter compound possesses the structure I,

I. 

II. 

thus proving that, during the ethylation, part of the resorcinol reacted in the keto-enolic form. In other words, we have here an example of the *tautomerism of resorcinol*. Resorcinol combines with sodium bisulphite to give a product which is in all probability the bisulphite compound of 3 : 5-*diketo-hexamethylene*-1-*sulphonic acid*. The formation of this substance may be explained [1] on the assumption that it is derived from the tautomeric form of resorcinol, II.

n-**Hexylresorcinol**, *Caprokol*, (OH : OH : C_6H_{13}=1 : 3 : 4), is a valuable internal antiseptic of high germicidal value [2] (*cf.* p. 357).

Hydroquinone, *quinol*, p-*dihydroxy-benzene*, m.p. 169°, is prepared by reducing quinone with sulphurous acid, and by virtue of its reducing properties is used as a photographic developer. With oxidising agents it is easily converted into quinone. Sodium bisulphite unites with hydroquinone to give 1:4-*dihydroxy-hexamethylene*-1:2:4-*trisulphonic acid*.[3] This reaction, as well as certain changes which take place in the hydroquinone developer, are explained on the assumption that hydroquinone may also react in tautomeric form as an unsaturated cyclic ketone.

Of the six dihydroxy-toluenes, $CH_3.C_6H_3(OH)_2$, the most important is **orcinol**, 3 : 5-*dihydroxy-toluene*, which may be regarded as a homologue of resorcinol. It occurs in the free and combined state in many lichens of the Roccella and Leconora families, and may be obtained from *orsellinic acid* by boiling with lime, or synthetically from acetone-dicarboxylic ester. Orcinol crystallises with 1 mol. H_2O in colourless prisms, m.p. 107° and b.p. 290°. When exposed to the air in ammoniacal solution it is transformed into *orceïn*, $C_{28}H_{24}N_2O_7$, a reddish-brown amorphous powder which forms the chief constituent of the dye *orseille* (French purple). Closely related to orceïn is the dye *litmus*, which is also prepared from lichens of the above varieties.

3. Trihydric Phenols and their Derivatives

All of the three possible isomerides expected on theoretical grounds are known, viz., pyrogallol, phloroglucinol and hydroxy-hydroquinone.

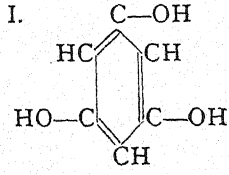
Pyrogallol, *pyrogallic acid*, 1:2:3-*trihydroxy-benzene*, is prepared by heating gallic acid, $C_6H_2(OH)_3.COOH=C_6H_3(OH)_3+CO_2$. It forms

[1] W. Fuchs and Elsner, *Ber.*, 1920, **53**, 886; 1924, **54**, 1225. [2] Johnson and Lane, *J. A. C. S.*, 1921, **43**, 348; Dohme, Cox and Miller, *ibid.*, 1926, **48**, 1688. [3] W. Fuchs and Elsner, *Ber.*, 1919, **52**, 2281.

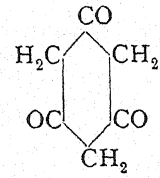
white plates, m.p. 132°, which dissolve readily in water. In alkaline solution it turns brown owing to absorption of oxygen, and hence is sometimes used for estimating oxygen in gas analysis.[1] Owing to its reducing properties it is also employed as a developer in photography.

Phloroglucinol, 1:3:5-*trihydroxy-benzene*, $C_6H_3(OH)_3$, melts at 218°, and is obtained as a disruption product of certain complex substances, *e.g.* from many resins by fusion with potash. It is best prepared from symmetrical triamino-benzene by heating with acids. Synthetically it may be obtained by Baeyer's method from sodio-malonic ester, which readily condenses to *phloroglucinol tricarboxylic ester*, $C_6(OH)_3(COOC_2H_5)_3$, and this on heating with alkalis yields phloroglucinol. Phloroglucinol is a tautomeric compound, reacting not only in the phenolic form, I, but also as a hexamethylene triketone, II.

I.



II.



Thus as a phenol it yields a trimethyl ether, $C_6H_3(OCH_3)_3$, and a triacetyl derivative, $C_6H_3(O.CO.CH_3)_3$, and as a ketone it forms a trioxime, $C_6H_3(NOH)_3$.

Hydroxy-hydroquinone, 1:2:4-*trihydroxy-benzene*, m.p. 140°, is produced in small amount when hydroquinone is fused with caustic soda. Its triacetate is easily obtained by warming quinone with acetic anhydride and concentrated sulphuric acid.

4. Polyhydric Phenols

Of these, only **hexahydroxy-benzene,** $C_6(OH)_6$, need be mentioned. The potassium salt of this compound, $C_6(OK)_6$, better known as potassium carbonyl, is obtained by leading carbon monoxide over heated potassium, and is also formed during the preparation of potassium from charcoal and potassium carbonate, when it occasionally gives rise to explosions. With hydrochloric acid the potassium salt yields hexahydroxy-benzene, a white crystalline substance which readily undergoes oxidation.

Corresponding to the thioalcohols and the alkyl sulphides are the **thiophenols,** *e.g.* $C_6H_5.SH$, and the **phenyl sulphides.** They are of little importance and cannot be described here.

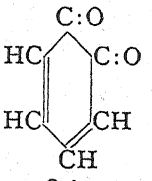
IX

Quinone and Quinonoid Derivatives

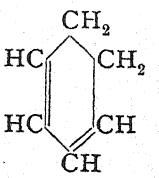
By quinones are understood compounds in which two hydrogen atoms of the benzene nucleus are replaced by two oxygen atoms, the products being distinguished as *o*- and *p*-quinones according to the relative positions of the substituents. Up to the present no *m*-quinone has been isolated, and *o*-quinones of benzene and its alkyl and halogen derivatives have

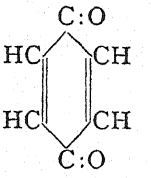
[1] For the chemical changes occurring during this reaction see Harries, *Ber.*, 1902, 35, 2954.

only been prepared in rare cases and for the most part comparatively recently. For this reason the *p*-compounds, which were the first to be discovered, were described shortly as quinones, and the name is still generally employed in this sense. The constitution of the benzoquinones is expressed in the formulæ I and II below, and that of other quinones

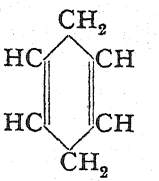
I. 

o-Quinone.

I*a*. 

II. 

p-Quinone.

II*a*. 

in a similar manner. It will be seen that they are represented as diketo-derivatives of an *o*- or *p*-dihydrobenzene (see I*a* or II*a*).

***o*-Benzoquinone, *o*-quinone,**[1] is obtained when catechol is oxidised with silver oxide. It exists in two solid modifications, one labile and crystallising in bright green needles, the other stable and crystallising in red, transparent plates.[2] Probably we are here dealing with dimorphous forms of the same substance, which are identical in solution but, owing to a difference in crystal structure, exhibit different colours in the solid state. *o*-Quinone is odourless and non-volatile. It decomposes on standing, and is reduced to catechol on treatment with sulphurous acid.

p-*Quinones* or *quinones*, of which the simplest representative is ordinary quinone, are formed by the oxidation of various *p*-disubstitution products of aromatic hydrocarbons. Most of them are yellow compounds of pungent smell, and are volatile in steam. They are readily reduced, taking up two atoms of hydrogen to form hydroquinones. They combine with two molecules of a monohydric phenol to give *phenoquinones*, and with one molecule of a dihydric phenol to yield dark-coloured addition compounds such as *quinhydrone* (see below).

Quinone, *benzoquinone*, $C_6H_4O_2$, was first obtained by the distillation of quinic acid with manganese dioxide and sulphuric acid, and is also formed by the oxidation of many *p*-disubstitution products of benzene (*e.g.* *p*-aminophenol, sulphanilic acid). It is usually prepared by oxidising aniline with sodium dichromate and sulphuric acid. Quinone forms golden-yellow crystals, m.p. 166°, possessing a peculiar, pungent smell; it is volatile in steam, colours the skin brown and is poisonous. With a

[1] Willstätter, *Ber.*, 1904, **37**, 4744. [2] Willstätter, *Ber.*, 1908, **41**, 2580; 1911, **44**, 2171. Kehrmann and Cordone, *Ber.*, 1913, **46**, 3009. S. Goldschmidt and F. Graef, *Ber.*, 1928, 61 B, 1858.

great variety of substances it unites to form addition products,[1] *e.g.* with hydroquinone it yields **quinhydrone**, $C_6H_4O_2$, $C_6H_4(OH)_2$. The latter crystallises in green prisms of metallic lustre, and occurs as an intermediate product in the reduction of quinone and the oxidation of hydroquinone; on further reduction it is transformed into hydroquinone, and on oxidation into quinone.

A volumetric estimation of quinones by means of titanous chloride is based on their ease of reduction [2]; in the case of quinone the reaction proceeds according to the equation

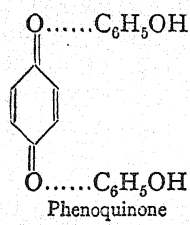
$$C_6H_4O_2+2TiCl_3+2HCl = C_6H_4(OH)_2+2TiCl_4$$

The quinone is dissolved in water and treated with an excess of standard titanous chloride solution, after which the unused titanous chloride is titrated with iron alum, using potassium thiocyanate as indicator.

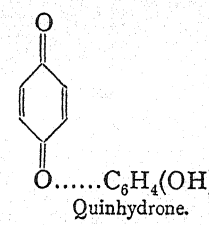
Tetrachloroquinone, chloranil, $C_6Cl_4O_2$, is produced by the chlorination of quinone, and also from a number of aromatic substances, such as phenol, by the action of chlorine or of potassium chlorate and hydrochloric acid. It is employed as an oxidising agent in the manufacture of dyes.

The Quinhydrones [3]

The simplest member of this group is the above-mentioned quinhydrone (Wöhler, 1884), the constitution of which has given rise to much discussion. It is now almost generally agreed that the quinhydrones are to be classed as molecular compounds. This view is confirmed more particularly by the work of Pfeiffer, from which it appears that in the quinhydrones the carbonyl oxygen atoms of the quinonoid components are united to the unsaturated carbon atoms of the benzenoid components. Since practically all quinhydrones, as well as the phenol-ether and hydrocarbon compounds of the quinones, are composed of 1 mol. quinone and 1 or 2 mols. of a benzenoid derivative, we are led to the assumption that each carbonyl oxygen atom can link up to one benzenoid molecule, as indicated in the following formulæ:



Phenoquinone



Quinhydrone.

The union is effected in such a manner that the subsidiary valency of the oxygen atom is saturated by a uniform field of affinity, which is produced by all, or at all events by the majority, of the unsaturated carbon atoms of the benzene derivative.

This conception enables us to represent graphically the close relation-

[1] For addition products of phenols and quinones, see K. H. Meyer, *Ber.*, 1909, **42**, 1149; 1910, **43**, 157. W. Schlenk, *Ann.*, 1908, **363**, 313; 1909, **368**, 271, 295. [2] E. Knecht and Hibbert, *Ber.*, 1910, **43**, 3455. See also Willstätter and Majima, *Ber.*, **43**, 1171. [3] Compare P. Pfeiffer, *Organische Molekülverbindungen*, edited by J. Schmidt (Enke, Stuttgart, 1927).

ship existing between quinhydrones, the coloured molecular compounds of nitro-derivatives, and the coloured additive compounds formed by ketones with acids and metallic salts.

Quinhydrones $\begin{cases} R_2C{=}O\cdots C_n\,H_m \\ R_2C{=}O\cdots C_n\,H_{m-1}.OH \\ R_2C{=}O\cdots C_n\,H_{m-1}.NH_2 \end{cases}$ Molecular Compounds of Nitro-derivatives $\begin{cases} R.NO_2\cdots C_n\,H_m \\ R.NO_2\cdots C_n\,H_{m-1}.OH \\ R.NO_2\cdots C_n\,H_{m-1}.NH_2 \end{cases}$

Halochromic Systems $\begin{cases} R_2C{=}O\cdots HX \\ R_2C{=}O\cdots MeX \end{cases}$

The connecting link between these organic molecular compounds and similar inorganic complexes is provided by the compounds formed by ketones with metallic salts. The latter stand in the closest relationship to two of the best-known groups of inorganic compounds of this type, viz., the double salts and the metallic ammines.

$R_2C{=}O\cdots\cdots SnCl_4$ $R_2C{=}O$ $\quad$ $KCl\cdots\cdots SnCl_4$ KCl $\quad$ $Am^1\cdots\cdots SnCl_4$ Am

QUINONOID COMPOUNDS

From *o*- and *p*-quinones [2] are derived a number of coloured substances, which are formed by the replacement of hydrogen or the ketonic oxygen by monovalent or polyvalent atoms or groups. Such compounds, which still contain the arrangement of linkings characteristic of the quinones (formulæ I and II, p. 434) are said to have a quinonoid structure.

For many reasons quinonoid compounds have attracted a considerable amount of attention from chemists. They are of importance not only in practice, for example many dyes belong to this class, but also from the theoretical standpoint. All these substances have a great tendency to change over from the quinonoid to the aromatic type (containing a benzene nucleus with three double bonds), and this tendency leads to remarkable movements of the side chains in the molecule. Thus it has been shown that the transformation of the quinol complex I into the corresponding aromatic structure may take place, according to experimental conditions, by the migration of either the hydroxyl or methyl group to another position in the nucleus.

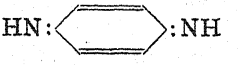
For example, 2 : 4-*dimethyl-quinol* II isomerises into p-*xylohydroquinone* III.

I. O= OH CH_3 II. CH_3 O= OH CH_3 $\longrightarrow$ III. CH_3 HO— —OH CH_3

[1] Am=amine. [2] The intense colour of these compounds may be ascribed to the fact that they are composed of four chromophore groups (see p. 72), viz., two C=C groups and two C=O groups.

Quinone-imines

These are derived from quinones by replacing one or both of the ketonic oxygen atoms by the imino-group : NH, or the alkyl- or arylimino group : NR. The simplest representatives of the class, *quinone-imine* (I) and *quinone-diimine* (II), have been prepared by Willstätter.[1]

I. II. 

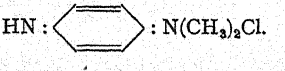
Quinone-imine (I) is obtained by the oxidation of *p*-aminophenol with silver oxide, $NH_2.C_6H_4.OH+O=NH:C_6H_4:O+H_2O$. It forms colourless crystals smelling like quinone, which rapidly darken in colour. It is extraordinarily unstable and decomposes quickly on lying in air. On warming for a short time with dilute sulphuric acid it is hydrolysed to quinone and ammonia. With stannous chloride and hydrochloric acid it is reduced to *p*-aminophenol. **Quinone-diimine** (II) is formed in similar manner by the oxidation of *p*-phenylene diamine, and by the reduction of quinone dichloro-diimine. It crystallises in colourless needles, melting about 124°, which are very unstable. With stannous chloride in acid solution it is readily reduced to *p*-phenylene diamine, and with dilute sulphuric acid it yields quinone and ammonia.

As already mentioned, both the above imines are colourless in the crystalline state, and by comparison with quinone and the fulvenes (p. 358) it would appear that, in contradiction to the view long held,[2] the group C:NH is a weaker chromophore than C:O or C:C.

Quinone-diimine is the parent substance of large classes of dye-stuffs, chief among which are the indamines and the azines.[3] Recently certain other types of dyes, particularly in the diphenyl- and triphenyl-methane series (to be dealt with later), have also been formulated in the same manner as the quinone-imines.

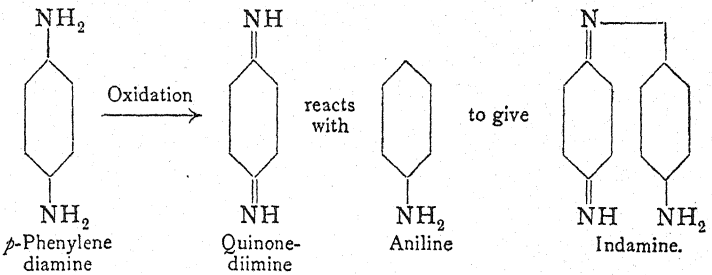
Indamines are most readily prepared by oxidising mixtures of monamines and *p*-diamines, or by the interaction of amines and quinone dichloro-diimine,[4] $ClN:C_6H_4:NCl$. In the former reaction it may be supposed that quinone-diimine is first produced, which then in the course

[1] *Ber.*, 1904, **37**, 1494, 4605; *Ber.*, 1905, **38**, 2244. [2] The investigation of the quinone-imines has also led to the discovery that certain quinonoid compounds can exist in both coloured and colourless forms (Willstätter, *Ber.*, 1905, **38**, 2244; Willstätter and Piccard, *Ber.*, 1908, **41**, 1458). In addition it is remarkable that whereas the simplest quinone-imines are colourless and give colourless salts, all the alkyl derivatives of *p*-phenylene diamine yield intensely coloured oxidation products which react as quinonimonium salts of the type of



[3] For the simplest quinonoid dyes, see J. Piccard, *Ann.*, 1911, **381**, 351. [4] **Quinone-chlorimine**, $O:C_6H_4:NCl$, and the above **dichloro-diimine** are best prepared by the oxidation of *p*-aminophenol hydrochloride or *p*-phenylene-diamine by means of hypochlorite solution.

of further oxidation reacts with the *p*-hydrogen atom of the amine as follows :—

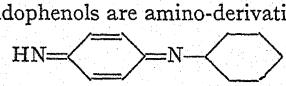


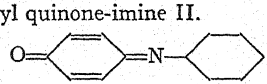
In confirmation of this, it is found that quinone-imine salts yield with amines intensely coloured solutions of indamines.

Indamines are also formed by the action of nitroso-dimethylaniline on amines.

Indamine, or **phenylene blue** (formula, see above), is obtained by the oxidation of an equimolecular mixture of *p*-phenylene-diamine and aniline, and is the simplest representative of the indamines. It forms greenish-blue salts, most of which are soluble in water, and with reducing agents is converted into *p*-diamino-diphenylamine. *Tetramethyl-indamine*, $C_{16}H_{19}N_3$, is obtained in a similar manner from dimethyl-*p*-phenylene-diamine and dimethylaniline. Its salts also dissolve to give green solutions, the hydrochloride being known as Bindschedler's Green.

The **indophenols** are closely related to the indamines, and are obtained by oxidising mixtures of phenols with *p*-diamines or *p*-aminophenols, or by the action of nitroso-dimethylaniline on phenols. Whereas indamines are amino-derivatives of phenyl quinone-diimine I, indophenols are amino-derivatives of phenyl quinone-imine II.

I. 

II. 

The only members of this class used technically as dyes are those prepared from *p*-phenylene-diamine in combination with phenol or α-naphthol. The latter is known as *α-naphthol blue.*

Certain heterocyclic compounds which give rise to important dye-stuffs, such as *phenazine* and *acridine* (see p. 700), may also be formulated as quinonoid derivatives.

Nitrosophenols and Quinonoximes

p-Nitrosophenols may be obtained by the following methods :—

1. By the action of nitrous acid on phenols.
2. By boiling *p*-nitroso-alkylamines with alkalis, *e.g.*,

$$ON.C_6H_4.N(CH_3)_2+KOH = ON.C_6H_4.OK+HN(CH_3)_2$$

3. By the interaction of hydroxylamine hydrochloride with quinones in aqueous or alcoholic solution.

These methods of preparation indicate the possibility of two constitutional formulæ for the nitrosophenols, *e.g.* for *p*-nitrosophenol,

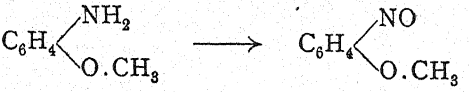
$HO.C_6H_4.NO$	$O:C_6H_4:N.OH$
p-Nitrosophenol	Quinone monoxime.

The nitroso formula is supported by methods 1 and 2 and also by the fact that nitric acid oxidises the nitrosophenols to nitrophenols.

On the other hand, the quinonoxime formula provides the best explanation of method 3, and of a number of other properties and reactions of the nitrosophenols, such as their weak basic character, the formation of quinone dioximes, *e.g.* $C_6H_4(NOH)_2$, when they are treated with hydroxylamine hydrochloride, and their conversion on methylation into methyl ethers of quinonoximes.

For these reasons it is assumed that we are here dealing with a case of tautomerism. Probably the free compounds correspond to the nitrosophenol formula, while their salts possess the oxime structure.

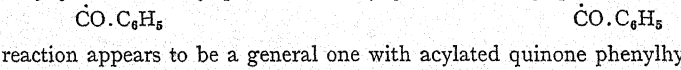
Methyl ethers of true nitrosophenols have been prepared by A. Baeyer and E. Knorr,[1] who found that anisidine could be oxidised by Caro's acid to give nitroso-anisole, *i.e.*, the methyl ether of the true nitrosophenol, a reaction similar to the oxidation of aniline to nitroso-benzene by means of the same reagent.



The *p*-compound has never yet been prepared entirely free from *p*-nitro-anisole, which is formed at the same time. On the other hand, ***o*-nitroso-anisole** is known in the pure state. When hydrolysed with a solution of acid potassium sulphate it yields ***o*-nitrosophenol.** In its reactions the latter strongly resembles *p*-nitrosophenol and hence is probably identical with the monoxime of *o*-quinone.

Hydroxy-azo-compounds and Quinone Phenylhydrazones

p-Hydroxy-azobenzene and other similar compounds are regarded as tautomeric substances; in no simple case has it been found possible to isolate both isomeric forms. Both types, viz., the quinone phenylhydrazone and the hydroxy-azo-compound, exist, however, in a series of derivatives. Thus the acyl derivatives of *p*-hydroxy-azobenzene and the corresponding isomeric acylated quinone phenylhydrazones are both known, and are formed by the action of unsymmetrical acyl-phenylhydrazines on benzoquinone. Quinone benzoyl-phenylhydrazone has been shown to undergo a peculiar intramolecular change when shaken in dry ethereal solution with powdered potassium hydroxide.[2] Under these conditions the benzoyl group moves to the oxygen atom standing in the *p*-position to the further nitrogen atom.



This reaction appears to be a general one with acylated quinone phenylhydrazones. Similar changes have been shown to occur with *o*-quinonoid derivatives of this type.[3] Since, then, the system I is immediately transformed into II,

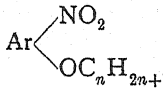
it would be contrary to all the established properties of tautomeric substances to assume that the parent compounds, *i.e.*, the hydrogen derivatives, should be stable in the quinonoid form. Hence it is concluded that *all the parent hydroxy-azo-compounds*

[1] *Ber.*, 1902, **35**, 3034. [2] R. Willstätter and Veraguth, *Ber.*, 1907, **40**, 1432. [3] K. Auwers, *Ber.*, 1907, **40**, 2154; *Ann.*, 1908, **360**, 11.

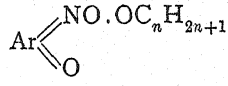
of this series, together with their ethers and esters, are true benzenoid azo-derivatives. It is only by using indirect methods that the quinonoid forms of a few of these compounds have been isolated, and of these only acyl derivatives of the *p*-series are known with certainty.

Tautomerism of the Nitrophenols

It has been shown by Hantzsch that *ethers of the nitrophenols* exist in two series, corresponding to the following formulæ :



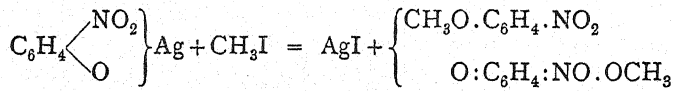
True nitrophenolic ethers
(benzenoid and colourless)



aci-Nitrophenolic ethers
(quinonoid and coloured).

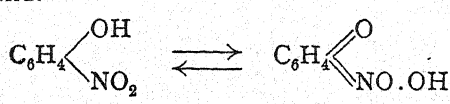
The parent nitrophenols, therefore, which are only known in one form, are to be classed as tautomeric.

The true nitrophenolic ethers have been known for a considerable time and are prepared by the usual methods of alkylation. The *aci*-ethers are obtained by alkylating the nitrophenol in the form of its silver salt under certain carefully chosen conditions, the true nitrophenolic ether being also produced at the same time.



The *aci*-ethers are intensely red in colour and are formulated as quinonoid compounds, in distinction to the colourless ethers of phenolic structure. *aci*-Ethers have much lower melting-points than their isomerides, and without exception are very unstable. Even at low temperatures, and when dissolved in indifferent solvents, they isomerise spontaneously with more or less speed into the true ethers. Further, they are very easily hydrolysed to nitrophenols, while the genuine nitrophenolic ethers only hydrolyse slowly.

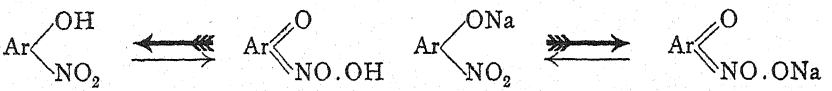
According to Hantzsch, it is possible to determine the condition or constitution of the parent nitrophenols directly from their colour.[1] Many nitrophenols, such as *p*-nitrophenol and 2 : 4-dinitrophenol, are colourless (or only faintly yellow) ; in the solid state such substances are consequently entirely (or almost entirely) true nitro-compounds. Others, such as the *o*-nitrophenols, are a little more strongly coloured, although never so intensely so as their esters. These are assumed to be solid solutions of a small amount of the coloured *aci*-nitrophenol in a large proportion of the true nitro-compound.



Thus ordinary yellow picric acid is supposed to be a solid solution of a little of the coloured quinonoid *aci*-trinitrophenol in much of the colourless trinitrophenol.[2]

[1] A. Hantzsch, *Ber.*, 1906, **39**, 1086. [2] *Cf.* also Georgievics, *Ber.*, 1906, **39**, 1536.

The salts of the nitrophenols with alkalis and alkaline earths are always much more highly coloured than the parent compounds; this indicates that the strongly acidic *aci*-form, barely traceable in the free substance, has been (almost) completely regenerated in the presence of the positive metallic atom, which always tends to attach itself to the most negative part of the molecule. Hence the equilibrium in the case of the free compounds is displaced almost completely in the direction of the phenolic form, and in the alkali salts equally completely towards the quinonoid form:



X

Aromatic Alcohols, Aldehydes and Ketones

When a hydroxyl group is introduced into the side chain of an alkyl benzene, an aromatic alcohol is formed such as benzyl alcohol, $C_6H_5.CH_2OH$. Compounds of this type may also be regarded as phenyl derivatives of the aliphatic alcohols, which they resemble in most respects. Like the fatty alcohols they may be obtained by heating the corresponding chloro-derivatives with water, by the reduction of aldehydes and ketones, by the action of nitrous acid on amines, and from organo-magnesium halides by combination with aldehydes, ketones or esters. The secondary and tertiary alcohols formed by this last method frequently pass by loss of water into benzene derivatives of olefins (see p. 382).

If we have at our disposal an alcohol, X.OH, or the corresponding halogen compound, X.Cl, there are three general methods available for synthesising homologues of the formula $X.CH_2OH$ or $X.CH_2Cl$ respectively: viz.,

1. Interaction of the halogen compound with potassium cyanide, hydrolysis of the nitrile X.CN to the acid X.COOH, esterification to $X.COOC_2H_5$ and reduction of the latter to the alcohol $X.CH_2OH$ (*Bouveault*).

2. Conversion of X.Cl into X.Mg.Cl, which with trioxymethylene yields the alcohol $X.CH_2OH$ (*Grignard*).

3. By forming the nitrile X.CN, reducing it to the amine $X.CH_2.NH_2$, and allowing the benzoyl derivative of the latter to interact with phosphorus chloride to give $X.CH_2.Cl$—a method which has been much used by J. v. Braun.[1]

Another useful means of preparing alcohols of this type is to shake

[1] J. v. Braun, Deutsch and Kruber, *Ber.*, 1911, 44, 2867.

the corresponding aldehyde with strong aqueous alkali[1] (*Cannizzaro* reaction).

$$2Cl.C_6H_4.CHO+KOH = Cl.C_6H_4.CH_2OH+Cl.C_6H_4.COOK$$

Benzyl alcohol, *phenyl carbinol,* $C_6H_5.CH_2OH$, occurs in the free state and in the form of esters in many ethereal oils. It is generally prepared from benzyl chloride by heating with alcoholic potassium acetate, and hydrolysing the benzyl acetate so obtained. It is a colourless liquid of faintly aromatic odour, boiling at 206°, and very sparingly soluble in water. With oxidising agents it yields benzaldehyde and finally benzoic acid. It forms ethers and esters, and on heating with hydrochloric or hydrobromic acid exchanges the hydroxyl group for chlorine or bromine.

Phenyl ethyl alcohol, $C_6H_5.CH_2.CH_2.OH$, b.p. 219°, is the chief constituent of natural and synthetic rose perfume.

Cinnamyl alcohol, *styrone,* or *γ-phenyl allyl alcohol,* $C_6H_5.CH:CH.CH_2OH$, is found as the cinnamic ester in *Storax*, and in the juice of the bark of *Liquidambar orientalis*. It is a crystalline compound, m.p. 33° and b.p. 250°, which smells of hyacinths. On gentle oxidation it yields cinnamic acid, and on vigorous oxidation benzoic acid.

Salicyl alcohol, *o-hydroxybenzyl alcohol, saligenin,* $HO.C_6H_4.CH_2OH$, is both an alcohol and a phenol, and is formed by the action of enzymes on *salicin*, a glucoside occurring in willow bark, $C_{13}H_{18}O_7+H_2O=C_6H_{12}O_6+C_7H_8O_2$. It crystallises in plates melting at 82°.

Aldehydes

The aromatic aldehydes resemble those of the fatty series in reactivity as well as in method of preparation. They may be obtained :

1. By oxidation of the corresponding primary alcohols.
2. From certain dichloro-compounds by heating with water, *e.g.*,

$$C_6H_5.CHCl_2+H_2O = C_6H_5.CH:O+2HCl$$

3. From alkyl derivatives of aromatic hydrocarbons by oxidation with chromyl chloride (*Etard's* reaction).

4. By reducing acid chlorides with hydrogen in the presence of palladised barium sulphate as catalyst.[2] Also by distilling the calcium salts of aromatic carboxylic acids with calcium formate, and by treating iminochlorides in ethereal solution with stannous chloride.[3]

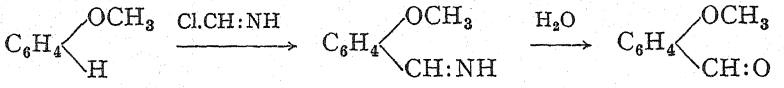
5. Indirectly by the *Friedel-Crafts* reaction, using carbon monoxide, hydrochloric acid gas and an aromatic hydrocarbon, in the presence of aluminium chloride (or aluminium bromide and cuprous chloride). Formyl chloride is formed as an intermediate product.[4]

$$R.C_6H_5+Cl.C\begin{matrix}O\\H\end{matrix} = R.C_6H_4.C\begin{matrix}O\\H\end{matrix}+HCl.$$

6. Similarly, by using HCN the aldehyde group may be introduced into phenols, phenolic ethers, or hydrocarbons (*Gattermann-Koch* reaction). The method consists in treating the phenolic compound with HCN and

[1] This reaction is said to be strongly catalysed by the addition of finely divided nickel. M. Delépine and A. Horeau, *C. r.*, 1937, **204**, 1605. [2] K. W. Rosenmund, *Ber.*, 1918, **51**, 585; 1923, **56**, 1481. [3] Sonn and Müller, *Ber.*, 1919, **52**, 1927. [4] Gattermann, *Ann.*, 1906, **347**, 347. H. Wolf, *Ber.*, 1928, **61**, 1765.

HCl, in some cases with the addition of condensing agents such as aluminium chloride or zinc chloride. Hydrogen cyanide first unites with hydrogen chloride to form the chloride of iminoformic acid,[1] which then reacts with the phenol, with elimination of hydrochloric acid, to give an aldoimine. The latter, on heating with dilute acids, is readily converted into the aldehyde itself.



7. Aldehydes are also produced from aromatic organo-magnesium compounds by treating these with formic or orthoformic esters,[2] *e.g.*,

$$CH_3.C_6H_4.MgBr+H.COOC_2H_5 = Br.Mg.OC_2H_5+CH_3.C_6H_4.CHO$$

Properties.—The aromatic aldehydes are usually pleasant-smelling liquids, which in their reducing properties and behaviour towards phenylhydrazine, hydroxylamine, and sodium bisulphite resemble the aliphatic aldehydes. They differ from the latter in certain points. For example, they do not polymerise, and on treatment with ammonia they do not yield additive compounds of the type of aldehyde ammonia (see benzaldehyde).

With alkali hydroxides they are converted into a mixture of an alcohol and the salt of a carboxylic acid (*Cannizzaro*), *e.g.*,

$$2C_6H_5.CHO+KOH = C_6H_5.CH_2OH+C_6H_5.CO_2K$$

Under the influence of potassium cyanide they undergo a peculiar reaction (see benzoin condensation). They also combine readily with various aldehydes, ketones, and mono- and dicarboxylic acids with the elimination of water, *e.g.*

$$\underset{\text{Benzaldehyde}}{C_6H_5.CHO}+\underset{\text{Acetaldehyde}}{H_3C.CHO} = \underset{\text{Cinnamic aldehyde.}}{C_6H_5.CH:CH.CHO}+H_2O$$

With dimethylaniline and with phenols the aromatic aldehydes condense to form triphenyl methane derivatives (see p. 513). On reduction with amalgamated zinc and hydrochloric acid the aldehydes are reduced to hydrocarbons (*Clemmensen's* method).

Benzaldehyde, *oil of bitter almonds,* $C_6H_5.CHO$, is formed from the glucoside *amygdalin* occurring in bitter almonds. When the glucoside is treated with the enzyme emulsin, or boiled with dilute acids, it decomposes into benzaldehyde, glucose and hydrogen cyanide :

$$C_{20}H_{27}NO_{11}+2H_2O = C_6H_5.CHO+2C_6H_{12}O_6+HCN$$

Benzaldehyde is employed in industry in the manufacture of dyes and perfumes, for which purpose it is generally prepared from benzal chloride (obtained from toluene) by heating with milk of lime. The

[1] Gattermann, *Ann.*, 1907, **357**, 313. According to L. E. Hinkel, E. E. Ayling and W. H. Morgan (*J. C. S.*, **1932**, 2793), the active agent is not the chloride of iminoformic acid but chloromethylene-formamidine, NH : CH . N : CHCl, produced by union of two molecules of HCN with one of HCl. For a simplification of this process, using zinc cyanide in place of hydrogen cyanide, see R. Adams and J. Levine, *J. A. C. S.*, 1923, **45**, 2373; **46**, 1518.

[2] Gattermann and Maffezzoli, *Ber.*, 1903, **36**, 4152. *Ann.*, 1906, **347**, 348.

product so prepared always contains admixed chloro-derivatives, and may thus be distinguished from natural oil of bitter almonds. It is a colourless liquid of characteristic smell, b.p. 179° and sp. gr. 1·050 at 15°. It is soluble in about 30 parts of water and mixes in all proportions with alcohol and ether. Benzaldehyde readily takes up oxygen, even on standing in air, to form benzoic acid. It unites with ammonia to give *hydrobenzamide*,

$$3C_6H_5.CHO+2H_3N = (C_6H_5CH)_3N_2+3H_2O$$

and with aniline to give *benzylidene-aniline*. Compounds of the latter type are known as **Schiff's bases** or **anils.**

$$C_6H_5.CHO+H_2N.C_6H_5 = C_6H_5.CH:N.C_6H_5+H_2O$$

Under the influence of alcoholic potassium cyanide it condenses to *benzoin*, a ketonic alcohol (see p. 524). When reduced with sodium amalgam the

$$C_6H_5.CH:O+H.CO.C_6H_5 = C_6H_5.CHOH.CO.C_6H_5 \text{ (Benzoin)}$$

latter yields the dihydric alcohol *hydrobenzoin*, $C_6H_5.CHOH.CHOH.C_6H_5$. The **oxime of benzaldehyde**, $C_6H_5.CH:NOH$, exists in two stereoisomeric forms (see below).

Stereoisomerism of the Aldoximes

Depending on the arrangement of the hydrogen atom and hydroxyl group about the double bond, aldoximes may exist in two isomeric modifications, which are known respectively as the *syn-* and *anti-* forms.

The problem of allotting to a given oxime the appropriate *syn-* or *anti-*configuration has proved more difficult than was at first suspected (see general section, p. 57). For the present it is convenient to adopt

R—C—H	R—C—H	R—C
‖	‖	|||
HO—N	N—OH	N
Anti-aldoxime	Syn-aldoxime	Nitrile.

the suggestion put forward by Brady and to classify these compounds as α- and β-aldoximes, according to the ease with which they may be converted by loss of water into the related nitrile.[1] The **α-form** on treatment with acetic anhydride at 30° yields an acetyl derivative which on hydrolysis with cold aqueous sodium carbonate regenerates the original oxime. Under the same conditions the **β-form** loses water and is converted into a nitrile or the corresponding acid. Recent research has thrown considerable doubt on the assumption made by Hantzsch, that owing to the spatial proximity of H and OH in the *syn*-form, this compound would pass into the nitrile more readily than the *anti*-form; and as a result of experiments on the ease of ring closure it is now believed that in general α-aldoximes are of the *syn-* and β-aldoximes are of the *anti-*configuration.

Aliphatic aldoximes are in general only stable in the β-form, and

[1] This classification is also accepted by Meisenheimer (see *Stereochemie*, by Freudenberg, p. 974).

their α-forms can rarely be isolated. Aromatic aldehydes yield α-aldoximes when treated with hydroxylamine, and these may frequently be transformed into the β-compounds by means of hydrogen chloride.

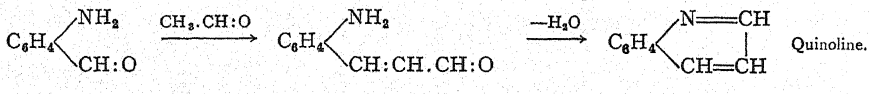
Thus benzaldehyde yields α-benzaldoxime (*benzsynaldoxime*), m.p. 35°, which with hydrochloric acid, sulphuric acid or bromine is converted into β-benzaldoxime (*benzantialdoxime*), m.p. 132°. When the latter is heated the reverse change occurs. These configurations are the opposite to those formerly assigned by Hantzsch.

p-*Isopropyl benzaldehyde, cuminol,* $(CH_3)_2CH.C_6H_4.CHO$, is the odorous constituent of oil of cumin. It is a colourless liquid of boiling-point 235°, which yields cymene when distilled with zinc dust.

Among **nitro-** and **amino-derivatives of benzaldehyde** the *o*-compounds are of importance, and are used in the preparation of various heterocyclic substances.

***o*-Nitrobenzaldehyde,** $NO_2.C_6H_4.CHO$, is formed in about 20 per cent. yield by the nitration of benzaldehyde. It is best obtained by the oxidation of *o*-nitrocinnamic acid, or by oxidising *o*-nitrobenzylaniline and hydrolysing the *o*-nitrobenzylidene-aniline so obtained. It forms colourless needles, m.p. 46°. In sunlight it readily isomerises into o-*nitrosobenzoic* acid, $ON.C_6H_4.COOH$. Its most important reaction is its conversion into indigo. In the presence of caustic soda it combines with acetone to give $NO_2.C_6H_4.CHOH.CH_2.CO.CH_3$, which readily loses water, yielding *o*-nitrobenzalacetone, $NO_2.C_6H_4.CH:CH.CO.CH_3$; on treatment with alkalis the latter immediately parts with acetic acid to form *indigo blue.* ***m*-Nitrobenzaldehyde,** m.p. 58°, is the chief product of the direct nitration of benzaldehyde. ***p*-Nitrobenzaldehyde** is obtained by boiling *p*-nitrobenzyl chloride with lead nitrate solution, and forms colourless prisms, m.p. 107°.

On reduction the above nitrobenzaldehydes are converted into the corresponding amino-compounds, $NH_2.C_6H_4.CHO$, of which the *m*- and *p*-derivatives are used in the preparation of dye-stuffs. ***o*-Aminobenzaldehyde,** m.p. 39°, is distinguished by the ease with which it unites with substances containing the group $—CH_2.CO—$, when water is eliminated and a derivative of quinoline formed, *e.g.*,



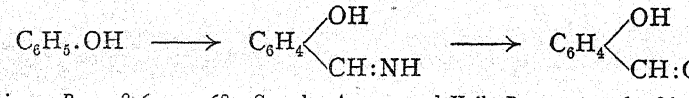
Hydroxy or Phenolic Aldehydes

The hydroxy-aldehydes, a number of which occur in nature, can be prepared by two methods.

1. When a phenol in alkaline solution is treated with chloroform, an aldehyde group is introduced into the *o*- or *p*-position to the phenolic hydroxyl [1] (*Reimer-Tiemann* reaction).

$$C_6H_5.OH+CHCl_3+4KOH = KO.C_6H_4.CHO+3KCl+3H_2O$$

2. In the presence of hydrogen chloride phenols react with hydrocyanic acid to form *aldo-imines*, which on boiling with dilute acids are readily converted into the corresponding hydroxy-aldehydes.[2] Aluminium chloride or zinc chloride is added in some cases as a condensing agent.



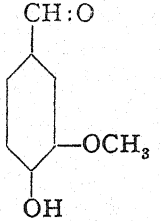
[1] Reimer, *Ber.*, 1876, **9**, 1268. See also Auwers and Keil, *Ber.*, 1903, **36**, 1861. [2] Gattermann, *Ber.*, 1898, **31**, 1149, 1765. *Ann.*, 1906, **347**, 347.

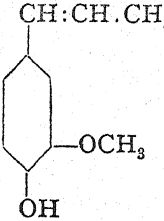
Phenolic aldehydes possess the properties of both phenols and aldehydes.

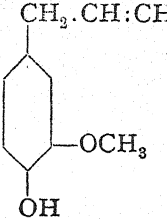
Salicylaldehyde, o-*hydroxy-benzaldehyde,* $HO.C_6H_4.CHO$, is found in the volatile oil of *Spiræa ulmaria,* and is prepared by oxidation of the corresponding alcohol saligenin, or together with *p*-hydroxy-benzaldehyde by the action of chloroform on an alkaline solution of phenol. It is a liquid, b.p. 196°, with a smell resembling that of benzaldehyde. On oxidation it yields salicylic acid, and like all *o*-hydroxyaldehydes colours the skin deep yellow.

Anisaldehyde, p-*methoxy-benzaldehyde,* $CH_3O.C_6H_4.CHO$, is formed by the oxidation of anethole, $CH_3O.C_6H_4.CH:CH.CH_3$ (occurring in oil of aniseed, fennel oil and oil of tarragon). It is a colourless liquid, b.p. 248°, which has an aromatic smell.

Vanillin, m-*methoxy*-p-*hydroxy-benzaldehyde* (I), is the active constituent of the vanilla pod, in which it is present to the extent of about 2 per

I. 

II. 

III. 

cent. It is the methyl ether of protocatechuic aldehyde, $C_6H_3(OH)_2.CHO$. On the industrial scale vanillin is prepared from the acetyl derivative of *isoeugenol* (II) by oxidising it with chromic acid to give acetyl vanillin, and subsequently removing the acetyl group from the latter. Isoeugenol is obtained from *eugenol* (III), the chief constituent of clove oil, by boiling with alcoholic potash.

Vanillin may also be prepared synthetically by the above general methods. It crystallises in colourless needles, m.p. 80°.

Piperonal, *methylene ether of protocatechuic aldehyde, heliotropin,* $C_6H_3\begin{cases}[1]\ CHO \\ [3]\ O \\ [4]\ O\end{cases}CH_2$, is formed when protocatechuic aldehyde is treated with alkali and methylene iodide, and is prepared from isosafrol by cautious oxidation with potassium bichromate and sulphuric acid. It possesses a very pleasant smell resembling that of heliotrope, and is placed on the market as a perfume under the name of heliotropin.

Cinnamic aldehyde, $C_6H_5.CH:CH.CHO$, is an example of an unsaturated aldehyde. It is found in oil of cinnamon and oil of cassia, to which it imparts the odour of cinnamon. From these sources it may be isolated by means of the sodium bisulphite compound. Synthetically it is obtained by the condensation of benzaldehyde with acetaldehyde (see Cinnamic Acid). It is an oil which boils at 246°.

Ketones

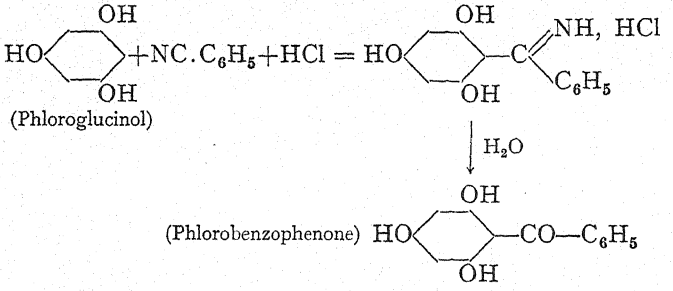
If two aromatic radicals are linked together by a CO-group the resulting compound is a purely aromatic ketone, such as benzophenone,

$C_6H_5.CO.C_6H_5$. Ketones containing one aliphatic and one aromatic radical attached to the carbonyl group are termed mixed or fatty-aromatic ketones.

Ketones of this type may be regarded as oxidation products of secondary aromatic alcohols. They are formed by the general methods available for ketones (p. 176), and also by the Friedel-Crafts reaction from acid chlorides and benzene in the presence of aluminium chloride.

$$\underset{\text{Benzene}}{C_6H_6}+\underset{\text{Acetyl chloride}}{CH_3.CO.Cl}=\underset{\text{Acetophenone.}}{C_6H_5.CO.CH_3}+HCl$$

Aromatic hydroxy-ketones may be prepared by the method of *Houben* and *Hoesch*[1] from polyhydric phenols. The latter, especially those containing hydroxyl groups in the *m*-position to each other, readily react with aliphatic or aromatic nitriles in the presence of hydrogen chloride to form ketiminochlorides, which on boiling with water yield the corresponding ketones, *e.g.*,



This reaction may be regarded as an extension of *Gattermann's* aldehyde synthesis (p. 439).

Aromatic ketones undergo the same typical reactions as those of the fatty series, but, in agreement with the "steric hindrance" observed by V. Meyer in connection with the esterification of acids, it is found that no oximes or hydrazones are formed by *o*-disubstituted aromatic ketones[2] of the formula $(CH_3)_2C_6H_3$—CO—R (in which R is an alkyl radical). Aliphatic-aromatic ketones may be reduced to hydrocarbons by use of Clemmensen's method (*q.v.*).

Acetophenone, *phenyl methyl ketone*, $C_6H_5.CO.CH_3$, is prepared by distilling an equimolecular mixture of calcium acetate and calcium benzoate, or by the interaction of acetyl chloride and benzene in the presence of aluminium chloride (Friedel-Crafts reaction). It crystallises in large plates, m.p. 20°, b.p. 202°, and is used as a hypnotic under the name of *hypnone*. When warmed with halogens, acetophenone undergoes substitution in the side chain. **Phenacyl bromide,** *ω-bromoacetophenone*, m.p. 50°, prepared in this way, is a lachrymatory compound which is useful in synthetic work.

Benzophenone, *diphenyl ketone*, $C_6H_5.CO.C_6H_5$, b.p. 307°, may be

[1] K. Hoesch, *Ber.*, 1927, **60**, 389, 2537; J. Houben, *Ber.*, 1928, **61**, 1597. [2] Baum, *Ber.*, 1895, **28**, 3207. V. Meyer, *Ber.*, 1896, **29**, 830, 2564.

obtained by the usual methods and is best prepared by the Friedel-Crafts reaction. It exists in two solid modifications, a stable form, m.p. 49° and a labile form, m.p. 27°. The latter readily changes into the former. Benzophenone on reduction yields the secondary alcohol **benzhydrol**, $C_6H_5.CHOH.C_6H_5$, m.p. 68°, and finally *diphenylmethane*, $C_6H_5.CH_2.C_6H_5$ (see p. 502). When fused with potash it decomposes into benzene and benzoic acid,

$$C_6H_5.CO.C_6H_5+KOH = C_6H_5.COOK+C_6H_6$$

In its other chemical properties, *e.g.* in its behaviour towards hydroxylamine, phenyl hydrazine and phosphorus pentachloride, it completely resembles the aliphatic ketones. When treated in alcoholic solution with dry hydrogen chloride and carbon disulphide, benzophenone yields **thiobenzophenone,**[1] $(C_6H_5)_2CS$, a deep violet crystalline compound, m.p. 51° to 52°.

p-**Diamino-benzophenone,** $CO(C_6H_4.NH_2)_2$, m.p. 237°, is formed when fuchsin is boiled with hydrochloric acid.

p-**Tetramethyl-diamino-benzophenone,** *Michler's ketone*, is prepared by the action of carbonyl chloride on dimethylaniline.

$$2C_6H_5.N(CH_3)_2+COCl_2 = CO[C_6H_4N(CH_3)_2]_2+2HCl$$

By further condensation with dimethylaniline it yields *Crystal Violet*, and with phenyl-α-naphthylamine it gives *Victoria Blue* (a wool dye). On reduction it passes into the corresponding alcohol *p*-**tetramethyl-diamino-benzhydrol,** $CHOH[C_6H_4N(CH_3)_2]_2$, which is also employed in the preparation of dye-stuffs.

Ketenes.—The ketenes (see p. 189) are compounds of the general formula $R_2C:CO$. **Diphenyl-ketene,** $(C_6H_5)_2C:CO$, the first member of the group to be prepared, was obtained by Staudinger [2] from diphenyl-chloracetyl chloride $(C_6H_5)_2CCl.COCl$, by the removal of chlorine with zinc. Diphenyl-ketene is a highly coloured and strongly unsaturated substance. It is very reactive and undergoes oxidation in air.

XI

Aromatic Carboxylic Acids

Aromatic acids are found free and in the combined state in many resins and balsams. They may be prepared by methods similar to those used for aliphatic acids, and by a number of special reactions, of which the following are the most important.

1. By oxidation of aromatic hydrocarbons and other benzene

[1] H. Staudinger and Freudenberger, *Ber.*, 1928, **61**, 1577, 1837. [2] Staudinger, *Ber.*, 1905, **38**, 1735; 1906, **39**, 968. *Ann.*, 1907, **356**, 51. *Ber.*, 1908, **41**, 1355, 1493; 1911, **44**, 533; 1913, **46**, 1437. G. Schroeter, *Ber.*, 1909, **42**, 2346.

derivatives containing side chains, when the latter are converted into carboxyl groups.

$$\underset{\text{Toluene}}{C_6H_5.CH_3}+3O = \underset{\text{Benzoic acid.}}{C_6H_5.COOH}+H_2O$$

A compound with one side chain attached to the nucleus oxidises to a monocarboxylic acid, while the presence of two or three side chains leads to the formation of di- or tricarboxylic acids respectively.

2. From salts of sulphonic acids by fusion with sodium formate.

3. In a similar manner to aliphatic acids by the hydrolysis of nitriles. The latter are most conveniently prepared from diazonium salts (see p. 404), or by the interaction of benzene-sulphonates with potassium cyanide.

4. Acid chlorides can be prepared by the action of phosgene or oxalyl chloride [1] on benzene and its derivatives in the presence of aluminium chloride (Friedel-Crafts).

$$C_6H_6+ClCOCl = \underset{\text{Benzoyl chloride.}}{C_6H_5.COCl}+HCl$$

5. Dry carbon dioxide reacts with a mixture of sodium, mercury (or zinc) diethyl, and benzene to form benzoic acid.[2] Homologues of benzene behave similarly, *e.g.* *o*-xylene yields *o*-tolyl-acetic acid.

Aromatic carboxylic acids are usually solid crystalline compounds which are sparingly soluble in water. Like the fatty acids they form chlorides, amides, esters and other derivatives. Further, by substitution in the benzene ring there may be obtained nitro-, amino-, chloro- and other derivatives which are dealt with in more detail later.

I.—MONOBASIC ACIDS

1. Benzoic Acid and its Homologues

Benzoic acid, $C_6H_5.COOH$, is found in gum benzoin, in Peru and Tolu balsams, and is present in the form of hippuric acid in the urine of horses. Originally it was prepared by heating gum benzoin, when the acid sublimes, or from hippuric acid, which on boiling with mineral acids is hydrolysed to glycine and benzoic acid. It is still obtained from gum benzoin for pharmaceutical purposes ("acidum benzoicum ex resina"), but otherwise is prepared almost exclusively from toluene. The latter is first converted into benzo-trichloride by treatment with chlorine at the boiling-point, and this is hydrolysed with milk of lime to give calcium benzoate, from which benzoic acid is precipitated by the addition of hydrochloric acid and purified by recrystallisation from water.

$$C_6H_5.CH_3 \xrightarrow{Cl} C_6H_5.CCl_3 \xrightarrow{Ca(OH)_2} (C_6H_5COO)_2Ca \xrightarrow{HCl} C_6H_5.COOH$$

A comparatively small amount of benzoic acid is also prepared by hydrolysis of the benzonitrile present in the middle oil from coal tar, $C_6H_5.CN \longrightarrow C_6H_5.COOH$.

[1] C. Liebermann, *Ber.*, 1911, 44, 202, 1186. [2] P. Schorigin, *Ber.*, 1908, 41, 2723; 1910, 43, 1938.

Benzoic acid crystallises in colourless glistening plates, and has a faint aromatic smell. It melts at 121°, boils at 250°, very readily sublimes and is volatile in steam. Although only sparingly soluble in cold water, it dissolves readily in the hot liquid, and also in alcohol and ether.

Salts of ammonia and the alkali metals are soluble in water, but most of the others are insoluble. When heated with lime, benzoic acid is decomposed into benzene and carbon dioxide. It is employed in medicine and in the manufacture of aniline blue.

Benzoyl chloride, $C_6H_5.COCl$, is prepared by warming the acid with phosphorus pentachloride or by the action of chlorine on benzaldehyde. It is a colourless liquid, b.p. 199°, with an unpleasant, pungent smell. In behaviour it resembles acetyl chloride, though differing in its greater stability as shown by the slowness with which it is attacked by water. Benzoyl chloride is frequently used as a means of introducing the benzoyl group, $C_6H_5.CO—$, into hydroxy-, amino- and imino-compounds. This is usually effected by shaking the substance with benzoyl chloride and excess of dilute sodium hydroxide until the smell of the former has disappeared (*Schotten-Baumann reaction*), *e.g.*,

$$\underset{\text{Phenol}}{C_6H_5.OH} + C_6H_5.CO.Cl = \underset{\text{Phenyl benzoate.}}{C_6H_5.CO.O.C_6H_5} + HCl$$

In many cases it is better to use sodium carbonate or pyridine in place of sodium hydroxide.

Benzoyl peroxide, $C_6H_5.CO.O.O.CO.C_6H_5$, may be obtained in various ways, such as by treating benzoyl chloride in water at 4° with the equivalent amount of sodium peroxide. It is odourless and crystallises in stable white prisms, m.p. 103·5°, which dissolve very sparingly in water, but more readily in alcohol. It is a strong disinfectant and has recently been utilised in this capacity.

Ethyl benzoate, $C_6H_5.COOC_2H_5$, prepared by the usual methods, is a pleasant-smelling liquid of boiling-point 213°.

For the peculiar behaviour of *o*-substituted benzoic acids on esterification see p. 374.

Benzamide, $C_6H_5.CO.NH_2$, is obtained by the action of ammonia or ammonium carbonate on benzoyl chloride. It crystallises in white plates, m.p. 130°, b.p. 288°. When silver benzamide is treated with ethyl iodide it forms the benzimino-ether (IV) instead of the expected ethyl benzamide (III). Hence benzamide is tautomeric and may react according to either of the formulæ I or II.

I. $C_6H_5.C(=O)NH_2$ II. $C_6H_5.C(OH)=NH$ III. $C_6H_5.C(=O)NH(C_2H_5)$ IV. $C_6H_5.C(OC_2H_5)=NH$

On the other hand, ethyl benzimino-ether (IV) isomerises into ethyl benzamide (III) on being heated to 100° with ethyl iodide.

Hippuric acid, benzoyl-aminoacetic acid, $C_6H_5.CO.NH.CH_2.CO_2H$ has been mentioned on p. 224. It occurs in the urine of herbivorous animals, and may be prepared from benzamide and chloracetic acid or by the benzoylation of glycocoll. It crystallises in rhombic prisms, m.p.

187°, and on boiling with alkalis or acids is hydrolysed into benzoic acid and glycocoll.

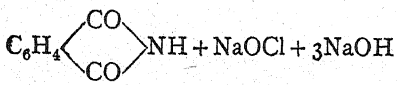
Benzonitrile, *cyanobenzene*, $C_6H_5.CN$, is best prepared by heating potassium benzene sulphonate with potassium cyanide. It is an oil, b.p. 191°, with a smell like bitter almonds. In its properties it resembles the fatty nitriles.[1] With sulphuric acid and other condensing agents it polymerises to *cyaphenin*, $C_3N_3(C_6H_5)_3$.

Substituted Benzoic Acids

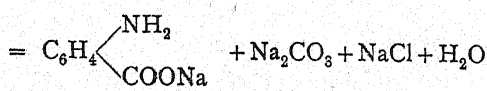
Chlorine reacts with benzoic acid mainly to form m-*chlorobenzoic acid*, m.p. 153°. The *o*- and *p*-compounds (m.p. 137° and 240°) are obtained from the amino-acids by way of the diazonium salts. Chlorine increases the strength of benzoic acid, the effect being greatest in the *o*- and least in the *p*-position.

On nitration benzoic acid yields m-*nitrobenzoic acid*, m.p. 141°, the other isomerides also being formed in smaller amounts. The *o*-compound, which is best prepared from *o*-nitrotoluene by oxidation, has a sweet taste and melts at 147°. The *p*-acid from *p*-nitrotoluene melts at 238°.

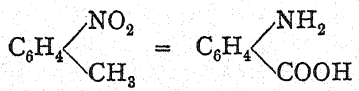
Among the *aminobenzoic acids*, which possess basic as well as acidic character (see Glycocoll), the most important is the ortho-compound, **anthranilic acid**, m.p. 145°, first obtained by fusing indigo with alkali. It is an important intermediate product in the technical preparation of indigo (described later), for which purpose it is produced in large quantities by the *Hofmann* reaction (p. 169) from phthalimide and chloride of lime or sodium hypochlorite.



Phthalimide

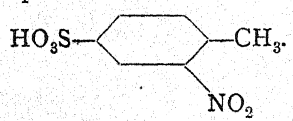


Other methods have recently been developed for preparing this compound. One of these is based on a peculiar change undergone by *o*-nitrotoluene, which when heated with aqueous or alcoholic sodium hydroxide is directly converted into anthranilic acid.[2]



o-Nitrotoluene Anthranilic acid.

The intramolecular rearrangement occurs particularly easily in the case of the nitrotoluene sulphonic acid of the formula



[1] Many *o*-substituted benzonitriles are difficult to hydrolyse by ordinary reagents, but give excellent yields of acids when heated with anhydrous phosphoric acid, S. C. J. Olivier, *Rec. trav. chim.*, 1929, **48**, 568. [2] Preuss and Binz, *Z. ang. Ch.*, 1900, **16**, 385.

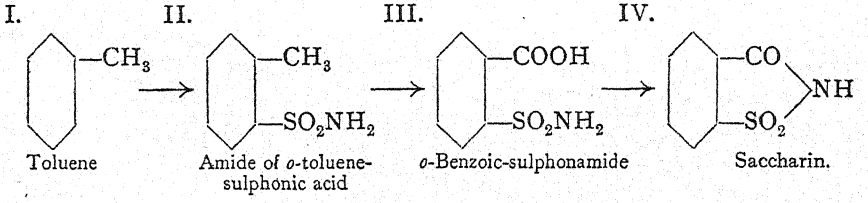
This yields the corresponding sulphonated anthranilic acid, from which the sulphonic group is readily removed by electrolytic reduction in neutral or slightly acid solution, with production of anthranilic acid.[1]

Anthranilic acid and its alkyl- or aryl-substitution products can also be prepared from *o*-chlorobenzoic acid, by treatment with ammonia or amines in the presence of copper powder.

The acid is soluble in water and alcohol, possesses a sweet taste, and on being heated readily decomposes into aniline and carbon dioxide. *Methyl anthranilate*, $NH_2.C_6H_4.COOCH_3$, m.p. 25°, is contained in the oils of orange blossom and *tuberosa* blossom.

Certain derivatives of the aminobenzoic acids are of physiological interest.[2] It has already been mentioned that all aromatic esters are capable of inducing local anæsthesia, and among the numerous amino-alkyl esters of aromatic amino- and polyamino-acids which have been prepared, one of these, viz., the *diethylamino-ethyl ester* of p-*aminobenzoic acid*, is so effective that it is used in the form of its hydrochloride, $NH_2.C_6H_4.COO.CH_2.CH_2.N(C_2H_5)_2,HCl$, as a local anæsthetic in medicine and dentistry under the name of *novocaine*. It crystallises from absolute alcohol in needles, m.p. 156°.

The three sulphobenzoic acids, $SO_3H.C_6H_4.COOH$, are obtained from the three toluene sulphonic acids by oxidation with potassium permanganate. m-*Sulphobenzoic acid*, accompanied by a little *p*-compound, is the chief product of the sulphonation of benzoic acid. The *imide of* o-*sulphobenzoic acid* (IV) is 500 times sweeter than sugar, and is sold as a sugar substitute under the name of **saccharin.** It is manufactured from toluene (I), which by sulphonation gives *o*-toluene-sulphonic acid, the amide of which (II) yields saccharin on oxidation. The *o*-benzoic-sulphonamide (III) formed in the last stage immediately loses water :



Saccharin itself is only sparingly soluble in water, but owing to the presence of the imido-group it possesses acidic properties, and forms salts. The sodium salt, $C_6H_4\langle^{CO}_{SO_2}\rangle NNa$, dissolves readily in water and is about 400 times sweeter than sugar.

[1] See *J. C. S.*, 1904, A., i., 159. [2] A. Einhorn, *Ann.*, 1910, **371**, 125.

Homologues of Benzoic Acid and their Derivatives

Homologues of benzoic acid may be of two types, namely alkylated benzoic acids, $R.C_6H_4.COOH$, and phenyl-substituted aliphatic acids, $C_6H_5.R.COOH$. The former resemble benzoic acid more closely than the latter.

Cumic acid, p-*isopropyl-benzoic acid,* $C_3H_7.C_6H_4.COOH$, m.p. 116°, is formed by the oxidation of cymene (p. 381) or of cuminol, and is therefore prepared by oxidising oil of cumin with potassium permanganate.

Phenyl-acetic acid, $C_6H_5.CH_2.COOH$, m.p. 76°, is conveniently obtained from benzyl chloride by the Grignard reaction, and is also formed during the putrefaction of proteins.

$$C_6H_5.CH_2.Cl \xrightarrow{Mg} C_6H_5CH_2MgCl \xrightarrow{CO_2} C_6H_5.CH_2.COOH$$

Mandelic acid, *phenyl-glycollic acid,*[1] $C_6H_5.CHOH.COOH$, contains an asymmetric carbon atom, and hence occurs in two optically active forms and an inactive racemic form. The latter, m.p. 118°, may be obtained by the addition of HCN to benzaldehyde, and hydrolysing the cyanhydrin so produced by means of hydrochloric acid. It can be resolved into the active acids (m.p. 133°) by recrystallisation of the cinchonine salts. l-*Mandelic acid,* the naturally occurring form, is prepared by warming amygdalin with fuming hydrochloric acid. On oxidation mandelic acid yields *benzoyl-formic acid,* or *phenyl-glyoxalic acid,* $C_6H_5.CO.COOH$, m.p. 66°.

Phenyl-propionic acids, $C_6H_5(C_2H_4)COOH$. α-Phenyl-propionic acid, or *hydratropic acid,* $C_6H_5.CH(CH_3).COOH$, is a liquid, b.p. 265°, obtained by the reduction of atropic acid (see index). β-Phenyl-propionic acid or *hydrocinnamic acid,* $C_6H_5.CH_2.CH_2.COOH$, m.p. 47°, b.p. 280°, is formed by the reduction of cinnamic acid, $C_6H_5.CH:CH.COOH$, and is produced during the putrefaction of proteins.

Phenyl-alanine, *β-phenyl-α-amino-propionic acid,* $C_6H_5.CH_2.CH(NH_2).COOH$, m.p. 283° to 284°, occurs with asparagine in the embryo of vetch ; the *l*-form is produced by the putrefaction or hydrolysis of proteins such as silk fibroin, oxyhæmoglobin and casein. It may be prepared in the racemic form by reducing α-amino-cinnamic acid with sodium amalgam, or by the action of ammonia on phenyl-bromo-propionic acid. By making use of its benzoyl derivative, the *r*-acid may be resolved into its active components.

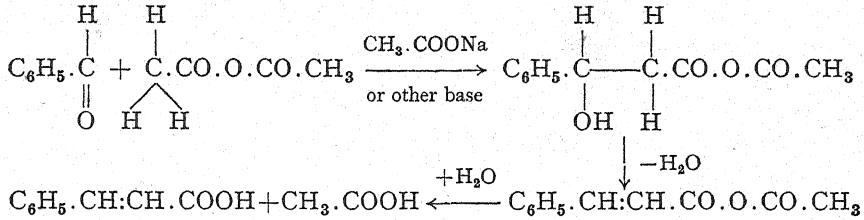
2. Monobasic Unsaturated Acids

Cinnamic acid, *β-phenyl-acrylic acid,* $C_6H_5.CH:CH.COOH$, is found free or as an ester in Peru and Tolu balsams and in storax. It can be prepared by a variety of methods.

1. By *Perkin's* reaction, in which benzaldehyde is condensed with

[1] Amino-phenyl-acetic acid, and phenyl-glycine are treated in connection with the indole group. For the configuration of mandelic acid see K. Freudenberg, *Ber.*, 1923, **56**, 193.

acetic anhydride in the presence of sodium acetate. The reaction possibly proceeds in the following stages [1]:



Perkin's reaction may be applied to the synthesis of numerous unsaturated acids and their substituted derivatives. In the above example benzaldehyde may be replaced by its homologues, its halogen- or nitro-substitution products, etc., and acetic anhydride by various other anhydrides.

2. By the *Claisen* condensation, using benzaldehyde and acetic ester in the presence of sodium ethoxide or metallic sodium,

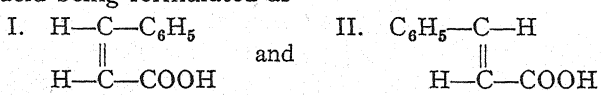
$$C_6H_5.CHO + H_3C.CO_2C_2H_5 \longrightarrow C_6H_5.CH:CH.CO_2C_2H_5$$

This reaction is also of general application.

3. Technically it is prepared from benzal chloride by heating with sodium acetate.

Cinnamic acid, m.p. 133°, b.p. 300°, crystallises from hot water in needles. It possesses the properties characteristic of ethylene derivatives, adding on bromine and hydrogen, and decolorising alkaline permanganate solution.

The cinnamic acids present an unusual case of isomerism. As explained on p. 48, ethylene derivatives can exist in two isomers of different space arrangement, the theoretical possibilities in the case of cinnamic acid being formulated as



In actual fact, however, there are in addition to ordinary cinnamic acid, which is assigned the *trans*-configuration II, no less than three *cis*-forms of the configuration I, namely:

1. Liebermann's *iso*-cinnamic acid, m.p. about 58°.
2. Erlenmeyer's *iso*-cinnamic acid, m.p. 42°.
3. Liebermann's *allo*-cinnamic acid,[2] m.p. 68°.

The last of these acids has been known for a considerable time, but the existence of the two *iso*-acids has been the subject of much discussion.[3] Liebermann's *iso*- and *allo*-cinnamic acids were first isolated as by-products during the preparation of cocaine. A mixture of these two

[1] C. R. Hauser and D. S. Breslow, *J. Amer. C. S.*, 1939, **61**, 786, 793. Reaction also occurs if sodium acetate is replaced by certain amines or by potassium carbonate (Kalnin, *Helv. chim. Acta*, 1928, **11**, 977). [2] Liebermann, *Ber.*, 1892, **25**, 950. Stoermer and Heymann, *Ber.*, 1912, **45**, 3099. [3] E. Erlenmeyer, jun., *Ber.*, 1905, **38**, 2562, 3496, 3499, 3891; 1906, **39**, 285, 1570; 1909, **42**, 2663. *Cf.* also Marckwald and Meth, *Ber.*, 1906, **39**, 1171.

acids with a small proportion of ordinary cinnamic acid was obtained later by Michael by the reduction of β-bromocinnamic acid (m.p. 159°). Eventually the researches of Biilmann [1] proved the separate existence of all three *cis*-acids, and also that, from the chemical point of view, they are not isomeric but identical. We are dealing here with a case of trimorphism, and in a few seconds any one of the three acids can be changed into any other, merely by melting it and seeding out the cooled melt with a crystal of the desired form. The *trans*-acid is partially converted into the *cis*-compound by illumination with ultraviolet light.

***o*-Nitrocinnamic acid,** m.p. 240°, is of interest in connection with the synthesis of indigo. It is formed together with the *p*-compound by treating cinnamic acid with concentrated nitric acid.

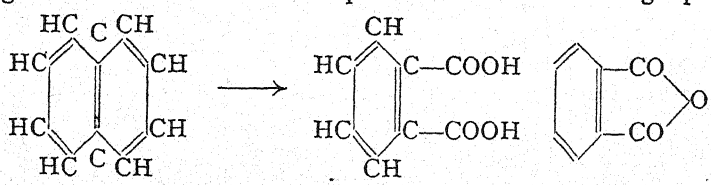
When the dibromide of *o*-nitrocinnamic acid is boiled with alcoholic potash it yields ***o*-nitrophenyl-propiolic acid,** $NO_2.C_6H_4.C:C.COOH$, which with reducing agents such as glucose and potassium hydroxide, hydrogen sulphide, or ferrous sulphate, is converted into indigo blue.

Atropic acid, *α-phenyl-acrylic acid,* $CH_2:C(C_6H_5).COOH$, m.p. 106°, is obtained from *tropic acid,* $CH_2OH.CH(C_6H_5).COOH$ (a disruption product of the alkaloids atropine and hyoscyamine) by heating with hydrochloric acid or baryta-water.

II.—POLYBASIC ACIDS

Polybasic aromatic acids may contain the carboxyl groups entirely in the nucleus, entirely in side chains (aryl-substituted fatty acids), or partly in the nucleus and partly in side chains. Chief among them, from the theoretical as well as the practical standpoint, are the dibasic phthalic acids. Reference is frequently made to these acids in determining the position of side chains in a benzene derivative, and the *o*-acid, ordinary phthalic acid, is also employed in the preparation of various dye-stuffs.

Phthalic acid, *benzene-o-dicarboxylic acid,* $C_6H_4(COOH)_2$, is the final oxidation product of a number of benzene derivatives containing two organic side chains in the ortho-position. It is used in large quantities



Naphthalene Phthalic acid Phthalic anhydride.

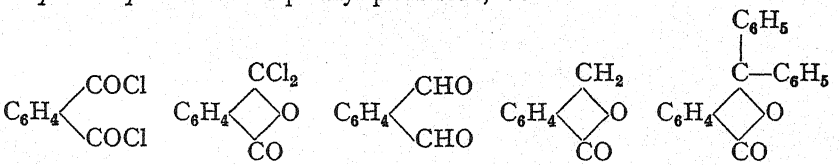
in the manufacture of indigo and other dyes, for which purpose it used to be obtained by heating naphthalene with fuming sulphuric acid, with the addition of mercuric sulphate as catalyst. During the oxidation sulphur trioxide becomes reduced to sulphur dioxide, $SO_3=SO_2+O$, which is recovered and converted into the trioxide.

[1] E. Biilmann, *Ber.*, 1909, **42**, 182. C. Liebermann, *Ber.*, 1909, **42**, 1027, 4659. De Jong, *C.*, 1919, **III**, 821. *Ber.*, 1922, **55**, 463. *C.*, 1922, **I**, 1023. *Ber.*, 1923, **56**, 818.

By the more recent process of Wohl and Gibbs phthalic anhydride is prepared technically in almost quantitative yield by passing naphthalene vapour and air over vanadium pentoxide at 450° to 520°.

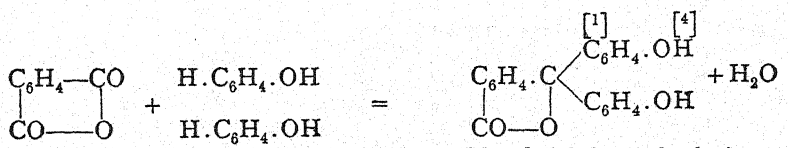
Phthalic acid crystallises in glistening plates, which are moderately soluble in hot water. When heated it loses water and passes into the anhydride.

Phthalic anhydride forms long needles, m.p. 128°, b.p. 285°. With phosphorus pentachloride it yields *phthalyl chloride*. From an examination of its optical refraction and absorption in ultraviolet light [1] phthalyl chloride has been assigned the symmetrical structure, I (see below). When treated with aluminium chloride [2] it is transformed into an isomeric modification, II. These two forms exhibit chemical as well as physical differences. The symmetrical chloride gives greenish-yellow solutions with guaiacol and with acenaphthene, whereas the unsymmetrical form remains colourless.[3] In this respect the two isomerides resemble phthalaldehyde, III, and phthalide, IV, the former of which is symmetrical and dissolves in dimethylaniline to give an orange-yellow colour, whilst the latter is unsymmetrical and yields a colourless solution. The chlorides also exhibit differences in other reactions. With zinc dust and acetic acid both phthalyl chlorides are reduced to phthalide, IV, and with benzene and $AlCl_3$ they form *phthalophenone* or diphenyl-phthalide, V.



I. II. III. IV. V.

Phthalic anhydride condenses with phenols to form triphenyl-methane dye-stuffs, which are known collectively as **phthaleïns.** The reaction proceeds by the *p*-hydrogen atoms of two molecules of phenol uniting with a carbonyl oxygen atom of anhydride to give water. The simplest of these compounds is *phenol phthalein*, formed as follows :—

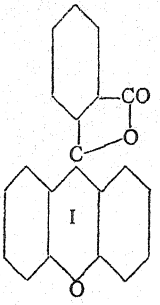


Phenol phthaleïn (colourless).

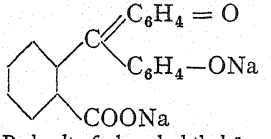
In the above condensation of phthalic anhydride with phenol the main reaction is accompanied by the formation of fluorane (formula on next page), which may be regarded as the parent substance of the fluoresceïns and rhodamines (see p. 454). In this case the two phenolic groups have condensed in the ortho- instead of the para-positions, and by the elimination of an additional molecule of water between the hydroxyl groups an oxygen ring, I (pyrone ring), has been formed.

[1] J. Scheiber, *Ber.*, 1912, **45**, 2252. [2] E. Ott, *Ann.*, 1912, **392**, 245. [3] P. Pfeiffer, *Ber.*, 1922, **55**, 413.

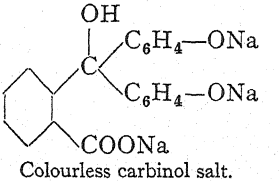
Phthaleïns may be considered as substitution products of the above-mentioned phthalophenone, which is the inner anhydride of triphenyl-carbinol-*o*-carboxylic acid. Many of them are of industrial value as dyes.



Phenol phthaleïn (formula, see p. 453) is prepared by heating phthalic anhydride and phenol to 120°, in the presence of concentrated sulphuric acid. It forms colourless crystals, which dissolve in alkali to give an intense red solution, from which the compound is precipitated in the colourless state by the addition of acids. On this colour-change depends its use as an indicator in volumetric analysis. The change of colour from colourless to red is assumed to coincide with a molecular rearrangement into the quinonoid form (compare the occurrence of colour in triphenyl-methane derivatives, pp. 510, 511). If a considerable excess of alkali is added the solution becomes colourless, probably owing to the production of a triphenyl carbinol salt formed by direct union of the quinonoid salt with sodium hydroxide. This series of changes is reversed on addition of acid.

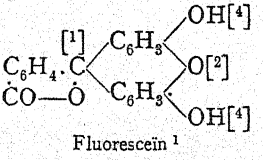


Red salt of phenol phthaleïn.

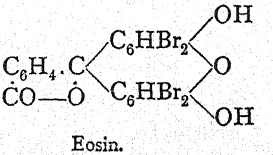


Colourless carbinol salt.

If in the above condensation resorcinol is used in place of phenol, the inner anhydride of resorcinol phthaleïn, or *fluoresceïn*, is formed (formula, see below). It is a dark yellow crystalline substance, soluble in alkalis to yellowish-red solutions, which, particularly when dilute, exhibit a magnificent green fluorescence. *This characteristic property of fluoresceïn and similarly constituted phthaleïns is used as a test for* meta-*dihydroxybenzene derivatives* (see p. 428) *as well as for phthalic anhydride.* Fluoresceïn is the starting-point in the preparation of most of the important dye-stuffs derived from phthalic acid. When treated with bromine, substitution occurs in the resorcinol groups with the formation, for example, of *tetrabromo-fluoresceïn*, $C_{20}H_8O_5Br_4$, the potassium salt of which is used industrially under the name of *eosin*. In a weakly acid bath the latter dyes wool and silk fine shades of red.



Fluoresceïn [1]



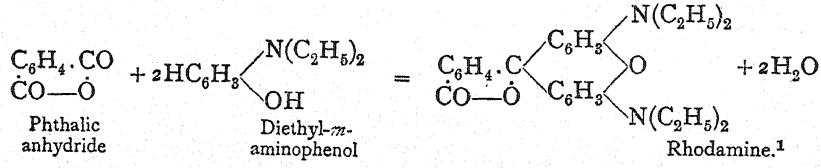
Eosin.

In place of phthalic anhydride its di- and tetrachloro-derivatives may

[1] The figures in brackets indicate the position of the substituents in the benzene nucleus.

also be fused with resorcinol, with the production of fluoresceïns which are chlorinated in the phthalic acid group. From these, by bromination and iodination, are prepared the dye-stuffs known as *Phloxines* and *Rose Bengals* respectively. The dyes obtained from chlorinated phthalic acids are distinguished from derivatives of ordinary fluoresceïn by a somewhat bluer shade of red, and are employed particularly in dyeing silk. *Galleïn*, prepared by fusing together phthalic anhydride and pyrogallol, is a violet dye, which with concentrated sulphuric acid at 200° yields *Coeruleïn*. The latter dyes green and is a derivative of phenyl anthracene.

The **Rhodamines**, another group of dyes, are phthaleïns of *m*-aminophenol and its N-alkylated derivatives. They are obtained by condensing phthalic anhydride with *m*-aminophenols, and are among the finest of the red dyes. The rhodamines may be regarded as diamino-derivatives of fluorane. Commercial rhodamine consists mainly of the phthaleïn of diethyl-*m*-aminophenol :



Phthalic anhydride — Diethyl-*m*-aminophenol — Rhodamine.[1]

Phthalimide, $C_6H_4\langle{}^{CO}_{CO}\rangle NH$, m.p. 238°, can be prepared by the action of ammonia on phthalic anhydride. It is used, on the one hand, for the technical preparation of anthranilic acid, and on the other for the production of primary aliphatic amines and primary amino-acids by Gabriel's method (see p. 220), which has also been modified by E. Fischer for the synthesis of diamino-acids [2] (*cf.* Ornithine). The synthesis of primary amines by this method is effected as follows.[3] Phthalimide reacts with alcoholic potash to form *potassium phthalimide*, $C_6H_4{:}(CO)_2{:}NK$, which when treated with alkyl halides exchanges the metallic atom for an alkyl radical. The alkyl phthalimide so obtained may be decomposed by heating with fuming hydrochloric acid, to give phthalic acid and a primary amine. The latter is obtained free from any admixed secondary and tertiary amines.

$$C_6H_4{:}(CO)_2{:}NK + IC_2H_5 = C_6H_4{:}(CO)_2{:}N.C_2H_5 + KI$$
$$C_6H_4{:}(CO)_2{:}N.C_2H_5 + 2H_2O = C_6H_4(COOH)_2 + C_2H_5.NH_2$$

A remarkable series of complex pigments has recently been prepared from phthalimide and from phthalonitrile. These are described later in connection with *Monastral Blue* (p. 646).

Isophthalic acid, *benzene*-m-*dicarboxylic acid*, $C_6H_4(COOH)_2$, results from the oxidation of benzene derivatives containing two carbon chains in the *m*-position, and may be prepared by oxidising *m*-xylene with calcium permanganate. It crystallises in

[1] In the rhodamines the NH_2 or $N(Alk)_2$ group occupies the *p*-position to the carbon atom of the phthalic residue. [2] E. Fischer, *Ber.*, 1906, **39**, 534. [3] For valuable improvements in this method see Ing and Manske, *J. C. S.*, 1926, **129**, 2348.

fine needles, m.p. 348°, which are difficultly soluble in water. It forms no anhydride. A derivative of isophthalic acid has already been mentioned in *uvitic acid* (see p 261).

Terephthalic acid, *benzene*-p-*dicarboxylic acid,* $C_6H_4(COOH)_2$, is formed in the same manner from *p*-disubstitution products of benzene, *e.g.* by the oxidation of *p*-xylene. It is obtained by the oxidation of oil of cumin (cymene+cuminol) as a white amorphous powder, which on being heated sublimes without melting. It also forms no anhydride.

Of the three isomeric *tricarboxylic acids* of benzene the most important is **trimesic acid** (1 : 3 : 5). It can be prepared from the corresponding trisulphonic acid, by conversion into the nitrile and subsequent hydrolysis. A more interesting synthesis is by polymerisation of the aliphatic compound propiolic acid. Trimesic acid sublimes about 200° and melts at 380°.

Mellitic acid, *benzene-hexacarboxylic acid,* $C_6(COOH)_6$, is present as its aluminium salt, $C_{12}Al_2O_{12}+18H_2O$, in peat. Owing to its yellow colour the salt is known as honey-stone. The acid is obtained by oxidising hexamethyl benzene with permanganate, and also from wood charcoal or graphite by oxidation with fuming nitric acid. It crystallises in fine white needles, decomposes on heating, and when distilled with lime yields benzene.

III.—PHENOLIC ACIDS

Aromatic hydroxy acids containing the hydroxyl group in an aliphatic side chain resemble in many ways the hydroxy-acids of the fatty series, and certain representatives of these aromatic alcohol-acids have already been mentioned. On the other hand, aromatic acids in which a hydroxyl group is attached to the nucleus combine the properties of an acid with those of a phenol, and are therefore described as phenolic acids. They may be obtained by a number of methods, of which the following are the most important.

1. From amino-acids by diazotisation and boiling the resulting diazo-compound with water.

2. By the fusion of sulphobenzoic acids with alkali hydroxides.

3. By the action of carbon dioxide on alkali phenoxides at high temperature (see Salicylic Acid).

4. By the interaction of carbon tetrachloride and phenols in alkaline solution :

$$C_6H_5OK+CCl_4+4KOH = C_6H_4(OH)CO_2K+4KCl+2H_2O$$

The carboxyl group tends to assume the *p*-position to the hydroxy group.

5. From benzene homologues or from phenols by fusion with caustic alkali and lead dioxide. In this manner *o*-cresol yields salicylic acid.

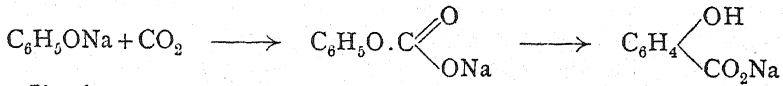
Monohydroxy-monocarboxylic Acids

1. *Hydroxy-benzoic Acids*

Salicylic acid, o-*hydroxy-benzoic acid,* $HO.C_6H_4.COOH$ occurs in the form of its methyl ester as the chief constituent of oil of wintergreen, from which it is isolated for therapeutic purposes. The corresponding phenolic alcohol, *saligenin* (see index), is a component of the glucoside salicin.

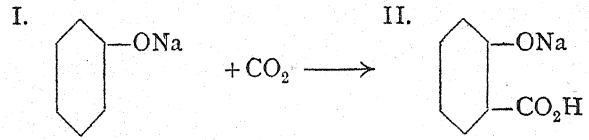
Salicylic acid may be formed by the above general methods, and is prepared technically by heating sodium phenoxide with carbon dioxide under pressure at about 140° (*Kolbe's* method).

For a long time this reaction was assumed to take the following course :



Phenol — Sodium phenyl carbonate — Sodium salicylate.

but as a result of later investigation [1] it appears that the simplest explanation is the correct one, the sodium phenate (I) combining directly with carbon dioxide, at the temperature employed, to form the sodium derivative of phenol-*o*-carboxylic acid (II).



Free salicylic acid is precipitated by the addition of mineral acid and recrystallised from hot water. It forms colourless needles, m.p. 155°, which dissolve sparingly in cold water, and readily in hot water or chloroform. In aqueous or alcoholic solution it gives a violet coloration with ferric chloride. It is employed as an antiseptic, particularly in the preservation of food, and is used in the preparation of dye-stuffs. Formerly it was used medicinally in cases of rheumatism, but it produces certain undesirable after-effects and has now been displaced by derivatives such as *aspirin* (acetyl salicylic acid), $CH_3CO.O.C_6H_4.COOH$ (m.p. 128°), having a milder action.

When salicylic acid is treated with an equivalent proportion of a phenol in the presence of phosgene or phosphorus oxychloride, esters are obtained. Thus *phenyl salicylate*, usually termed *salol*, $C_6H_4(OH)COOC_6H_5$, is prepared by the action of phosgene on a mixture of phenol and salicylic acid. It melts at 42°, and is used as an antiseptic. The β-naphthyl ester of salicylic acid, *betol*, $C_6H_4(OH)COOC_{10}H_7$, serves the same purpose, and the acetyl-*p*-aminophenyl ester, known as *salophene*, is used as a remedy for headache. Many esters of salicylic acid are employed as perfumes.

Meta- and *para-hydroxy-benzoic acids*, m.p. 200° and 210° respectively, can be prepared from the corresponding amino- and halogen-substituted benzoic acids. The acids are of little importance but some of their derivatives are of interest. *Methyl* p-*amino*-m-*hydroxy-benzoate*, m.p. 121°, is used as a local anæsthetic (under the name of *orthoform*), as is also the *m*-amino-*p*-hydroxy-derivative (*new orthoform*).

p-*Methoxy-benzoic acid*, *anisic acid*, $CH_3O.C_6H_4.COOH$, is formed by the oxidation of oil of aniseed, and may be prepared from *p*-hydroxybenzoic acid by methylation with methyl iodide and alkali, or from *p*-bromo-anisole by the Grignard reaction, using magnesium and carbon dioxide. It melts at 185°, and boils at 280°.

[1] See *Ber.*, 1905, **38**, 1375 ; 1906, **39**, 14.

2. *Monobasic Phenolic Acids with Carboxyl in the Side Chain, and the Coumarins*

***p*-Hydroxy-phenyl-propionic acid,** *hydrocoumaric acid*, $HO.C_6H_4.CH_2.CH_2.COOH$ (see p. 459), results from the putrefaction of tyrosine, and occurs in old cheese and in the pancreas. It is obtained by the hydrolysis of proteins and forms monoclinic crystals, m.p. 128°. The *α*-amino derivative of this acid is tyrosine.

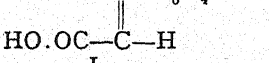
Tyrosine, p-*hydroxy-phenyl-alanine*, $HO.C_6H_4.CH_2.CH(NH_2).COOH$, occurs as the *l*-form (m.p. 314° to 318°) in old cheese, the berries of the elder, the spleen, the pancreatic gland and in diseased liver. It is also produced from many proteins by hydrolysis with dilute acids,[1] by pancreatic digestion, or by putrefaction. *r*-Benzoyl-tyrosine can be conveniently obtained by the method of Erlenmeyer, jun. *p*-Hydroxy-benzaldehyde, $HO.C_6H_4.CHO$, is condensed with hippuric acid, $H_2C(NH.CO.C_6H_5).COOH$, to give *p*-hydroxy-α-benzoylamino-cinnamic acid, $HO.C_6H_4.CH:C(NH.CO.C_6H_5).COOH$, which on reduction with sodium amalgam yields *r*-benzoyl-tyrosine, m.p. 192°. By crystallisation of the brucine and cinchonine salts E. Fischer succeeded in resolving this acid into *l*- and *d*-benzoyl-tyrosines (m.p. 162°). From the benzoyl derivatives *l*-, *d*- and *r-tyrosines* can be prepared by heating with hydrochloric acid. A physiologically important derivative of tyrosine is the hormone, *thyroxine* (p. 843).

Tyrosol, or p-*hydroxyphenyl-ethyl alcohol*,[2] is produced by the fermentation of tyrosine with sugar and compressed yeast.

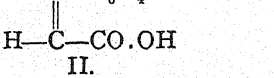
$$\underset{\text{Tyrosine}}{HO.C_6H_4.CH_2.CH(NH_2).CO_2H} \longrightarrow \underset{\text{Tyrosol.}}{HO.C_6H_4.CH_2.CH_2.OH}$$

Tyrosol crystallises in small, colourless needles, m.p. 93° and b.p. about 310°. It is a normal product of the protein metabolism of yeast and hence is a by-product of all kinds of yeast fermentations, being found in the majority of fermented beverages, particularly in beer and wine.

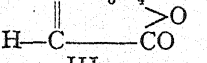
***o*-Hydroxy-cinnamic acid,** $HO.C_6H_4.CH:CH.COOH$, exists in two isomeric forms, distinguished as **coumarinic acid** and ***o*-coumaric acid** respectively. These acids bear the same relationship to one another as maleic and fumaric acids. In coumarinic acid (II) the groups $HO.C_6H_4$— and —COOH lie on the same side of the molecule (*cis*-form), and in coumaric acid (I) they are on opposite sides (*trans*-form).



I.



II.



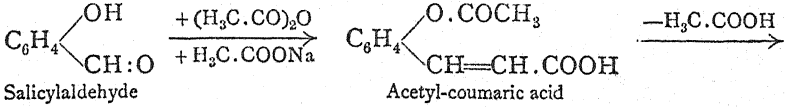
III.

The chief difference between these compounds is that coumarinic acid in aqueous or alcoholic solution is only stable in the form of its salts, and when liberated in the free state passes at once into the anhydride, *coumarin* (III). On the other hand, *o*-coumaric acid is readily obtained in the free state. *o*-Coumaric acid occurs in *melilotus officinalis*, and may be prepared from *o*-amino-cinnamic acid by way of the diazo-compound, or

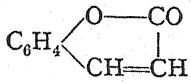
[1] See formation of *l*-tyrosine from silk fibroin, E. Fischer, *Z. physiol. Ch.*, 1901, **33**, 181.
[2] F. Ehrlich, *Ber.*, 1911, 44, 139.

from coumarin by boiling with sodium ethoxide. It melts at 208°, is readily soluble in hot water or alcohol, and on reduction with sodium amalgam yields o-*hydrocoumaric* or *melilotic acid*.

Coumarin (formula III above) is responsible for the perfume of the woodruff (*Asperula odorata*), and occurs also in melilot and in the Tonquin bean. It is prepared by Perkin's reaction (p. 450) by heating salicylaldehyde with acetic anhydride and sodium acetate.



Salicylaldehyde — Acetyl-coumaric acid



Coumarin.

Homologues of coumarin may be synthesised by the same method, using salts and anhydrides of propionic acid, butyric acid, and so on, in place of those of acetic acid.

Coumarin can also be obtained by the action of sulphuric acid on a mixture of phenol and malic acid (*von Pechmann*), and substituted coumarins from sulphuric acid, phenols and esters of acetoacetic or monoalkyl-acetoacetic acids.

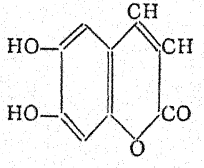
Coumarin is used in the preparation of perfumes (essence of woodruff) and perfumed tobacco.

Umbelliferone, 4-hydroxy-coumarin, HO.C_6H_3 , is found in the bark of

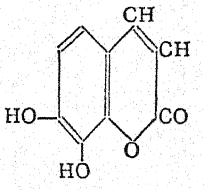
Daphne mezereum, and is produced by the distillation of resins obtained from a number of the *umbelliferæ*. It may be synthesised by Perkin's reaction from β-resorcyl-aldehyde, acetic anhydride and sodium acetate, or in a similar manner to coumarin from resorcin and malic acid. It melts at 240° and is the lactone of *p*-hydroxy-*o*-coumaric acid or *umbellic acid*, $(HO)_2C_6H_3.CH:CH.COOH$. A structural isomeride of this compound is *caffeïc acid*, 3 : 4-dihydroxy-cinnamic acid, the monomethyl ether of which, *ferulic acid*, may be converted into vanillin.

Among substitution derivatives of coumarin may be mentioned the structurally isomeric dihydroxy compounds *aesculetin* (I) and *daphnetin* (II).

I.



II.



The former is a disruption product of the glucoside *aesculin*, occurring in the horse chestnut, and the latter of the glucoside *daphnin*, found in members of the Daphne family. Aesculetin and daphnetin are prepared by Perkin's reaction, by heating hydroxy-hydroquinone-aldehyde and pyrogallic aldehyde respectively with acetic anhydride and sodium acetate.[1] They may be regarded as inner anhydrides (δ-lactones) of trihydroxy-cinnamic acids ; the latter are not stable in the free state, but only in the form of ether-acids or ether-esters.

[1] Gattermann and Eggers, *Ber.*, 1899, **32**, 289.

Di- and Trihydroxy-Monocarboxylic Acids [1]

Dihydroxy-acids may be derived from the three dihydric phenols, pyrocatechol, resorcinol and hydroquinone. All the six possible isomerides are known.

Protocatechuic acid, $C_6H_3\begin{cases}CO_2H[1]\\OH\ [3]\\OH\ [4]\end{cases}$, is formed from various resins (catechu, gum benzoin, myrrh and particularly kino) by fusion with alkali. It may also be obtained from pyrocatechol by heating it to 140° with ammonium carbonate. It crystallises with 1 mol. water, and in the anhydrous state melts at 199°, fusion being accompanied by decomposition into carbon dioxide and pyrocatechol. In aqueous solution protocatechuic acid gives with ferric chloride a green coloration, which on addition of sodium carbonate changes to blue, and finally to red.

According to theory, there should be six possible trihydroxy-benzoic acids, three of which are known.

Gallic acid, 3:4:5-*trihydroxy-benzoic acid,* $C_6H_2(OH)_3COOH$, is found in tea, nut-galls, the fruit of *Cæsalpina coriaria* (*Divi-divi*), the root of the pomegranate and in many other plants. It is usually prepared from tannin by boiling with dilute acids, and may be synthesised from bromo-dihydroxy-benzoic acid or bromo-protocatechuic acid by fusion with potash. It dissolves readily in alcohol, ether or boiling water, but is only sparingly soluble in cold water. From the latter it crystallises with 1 mol. H_2O. On heating to about 220° it decomposes into carbon dioxide and pyrogallol. Solutions of its alkali salts absorb oxygen from the air and become brown in colour. When gallic acid is treated with potassium persulphate in sulphuric acid it yields **ellagic acid,**[2] $C_{14}H_6O_8$. Gallic acid precipitates gold and silver from their salts and hence can be employed in photography. With ferric chloride it gives a blue-black precipitate. Basic bismuth gallate, $(HO)_3C_6H_2CO_2.Bi(OH)_2$, is used in medicine under the name of **dermatol,** as an odourless antiseptic in cases of injury or disease of the skin. Bismuth hydroxy-iodide gallate, $(HO)_3C_6H_2CO_2.Bi(OH)I$, is employed similarly under the name of **airol.**

Orsellinic acid, 4:6-*dihydroxy*-o-*toluic acid,* $CH_3.C_6H_2(OH)_2.CO_2H$ is of importance in connection with the chemistry of lichens, from which source it may be extracted. It is prepared by oxidising the readily obtainable orcyl aldehyde, or from the methyl ester of dihydro-orsellinic acid. On partial methylation with diazomethane it yields **everninic acid,** $CH_3O(4).C_6H_2.OH(6).CH_3(2).COOH(1)$, which is also produced by boiling *evernic* and *ramalic acids* (present in many lichens) with baryta. It forms colourless needles which on rapid heating melt with decomposition in the neighbourhood of 170°.

[1] Strictly speaking, the di- and trihydroxy-cinnamic acids discussed in the previous section should be included here. They are, however, more conveniently treated in connection with coumarin. [2] For the constitution of this acid see A. G. Perkin and Nierenstein, *Proc. Chem. Soc.*, 1905, **21**, 185. Herzig and Pollak, *Monats.*, 1908, **29**, 263. Graebe, *Ber.*, 1903, **36**, 212.

Depsides [1]

By the combination of phenol-carboxylic acids Emil Fischer synthesised a number of ester-derivatives which he named *depsides*, because of the resemblance many of them show to the tannins (δέφειν, to tan). According to the number of phenol-carboxylic acid molecules united together, these are distinguished as *di-*, *tri-*, *tetra-depsides*, and so on. The nomenclature is thus similar to that of the polysaccharides and polypeptides. A simple example of a di-depside is the anhydride of *p*-hydroxy-benzoic acid, formed by the phenolic hydroxyl of one molecule uniting with the carboxyl group of a second to yield the ester, $HO.C_6H_4CO—O.C_6H_4.COOH$ (depside of *p*-hydroxy-benzoic acid). In a similar manner a third molecule may enter into reaction to give the tri-depside $HO.C_6H_4.CO—O.C_6H_4.CO—O.C_6H_4.COOH$.

Fischer prepared the above compounds as the result of an observation made during the synthesis of polypeptides of tyrosine, for which the acid chloride of chloracetyl-tyrosine was required. It appeared probable that the free phenolic group of the acid might cause trouble owing to the necessary treatment with phosphorus chloride, and it was therefore protected by the introduction of another group which could later be removed without difficulty. For this purpose the carbomethoxy group was selected. Later the same process was applied to the phenol-carboxylic acids and led to the synthesis of depsides. In place of the carbomethoxy compounds first employed, Fischer later used acetylated phenol-carboxylic acids in this work.

Carbomethoxy Derivatives of Phenol-carboxylic Acids.—These are readily obtained by the combined action of methyl chloroformate and alkali on phenol-carboxylic acids in cold aqueous solution.[2] The reaction proceeds particularly smoothly when the phenolic group is in the *m*- or *p*-position to the carboxyl group, *e.g. p*-hydroxy-benzoic acid readily yields carbomethoxy-*p*-hydroxy-benzoic acid, $CH_3O.CO.O.C_6H_4.COOH$.

Chlorides of carbomethoxy-phenolcarboxylic acids are obtained by the action of phosphorus pentachloride on the acids. They are usually crystalline and have most of the properties of benzoyl chloride. Since the carbomethoxy group can easily be removed, they are of great value for further synthesis.

Conversion of the Chlorides into Depsides.—The acid chlorides may be combined with free phenol-carboxylic acids, and on subsequent removal of the carbomethoxy group di-depsides are produced. By repeating this process tri- and tetra-depsides may be obtained. For example, the chloride of carbomethoxy-*p*-hydroxy-benzoic acid unites with *p*-hydroxy-benzoic acid in the presence of cold aqueous alkali to form the salt of *carbomethoxy* p-*hydroxybenzoyl-hydroxy-benzoic acid*:

$$CH_3O.CO.O.C_6H_4.CO.Cl + NaO.C_6H_4.COONa = NaCl + CH_3O.CO.O.C_6H_4.CO.O.C_6H_4.CO_2Na$$

On treatment with mineral acid this salt yields the free acid.

[1] E. Fischer, *Ber.*, 1913, **46**, 3253; 1919, **52**, 809. P. Karrer and Salomon, *Helv., Chim. Acta*, 1922 **5**, 108; 1923, **6**, 3. [2] E. Fischer, *Ber.*, 1908, **41**, 2875.

Removal of the Carbomethoxy Group.—This may be effected by means of cold dilute alkali or ammonia.

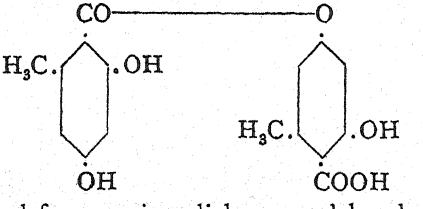
By these methods Fischer has prepared numerous depsides and some tri- and tetra-depsides, including the di-depsides, *lecanoric acid* and *evernic acid*, which are present in lichens.

Properties of Depsides.—All depsides are decomposed into their components by an excess of dilute alkali, even at the ordinary temperature. The di-depsides of gallic, protocatechuic, gentisic and β-resorcylic acids precipitate dilute solutions of glue, and give a precipitate with quinine acetate even at high dilutions. In this property they differ from the parent phenol-carboxylic acids and resemble the tannins.

Depsides in Lichens [1]

So far as is known, the lichens form the only natural source of depsides. Lichens are a result of the symbiosis (lit. *living together*) of algæ and fungi, and their peculiar morphological character goes hand in hand with their unusual chemical composition, as shown in their content of depsides. Among the latter the best known representative is lecanoric acid.

Lecanoric acid,[2] p-*di-orsellinic acid*, is a di-depside of the formula



It may be isolated from various lichens, and has been synthesised by methods already described from orsellinic acid. Lecanoric acid is sparingly soluble in water, but dissolves more readily in ether (1 : 30). In the dry state it melts with decomposition at about 166°.

Evernic acid, monomethyl-lecanoric acid, contains a methoxyl in the *p*-position to the depside group (see previous formula), since the everninic acid obtained (together with orsellinic acid) from it on hydrolysis has been shown to be *p*-methyl-orsellinic acid. It can be synthesised from everninic and orsellinic acids by the same methods as were used for lecanoric acid.

Gyrophoric acid is a naturally occurring tridepside. Its formula [3] is obtained by linking the free carboxyl group in lecanoric acid to the para-hydroxyl group of a molecule of orsellinic acid.

THE TANNINS [4]

Under this name are included numerous vegetable products possessing the common property of combining with animal hide to render it pliant

[1] E. Fischer, *Ber.*, 1913, **46**, 3269. A. Sonn, *Ber.*, 1928, **61**, 2479. [2] E. Fischer and H. O. L. Fischer, *Ber.*, 1913, **46**, 1138. [3] Y. Asahina and co-workers, *Ber.*, 1932, **65B**, 983, 1937, **70B**, 200. F. W. Canter, A. Robertson and R. B. Waters, *J. C. S.*, 1933, 493.
[4] Freudenberg, *Die Chemie der natürlichen Gerbstoffe*, Berlin, 1920.

and non-putrescible. When an attempt is made to classify these substances from the chemical standpoint it is found that they fall into a number of quite different groups. Those best investigated are the tannins of the tannic acid class, which may be described shortly as esters derived from sugars by union with phenol-carboxylic acids.

The typical and most important tannin is **tannic acid.** This is closely related to *gallic acid*, and is present in large amount (about 50 per cent.) in gall-nuts, which are pathological growths on the leaves and twigs of trees of the oak family, due to the puncturing of the tissues by the gall wasp. In addition it is found in sumach, tea and many other plants. It is best prepared from finely-divided gall-nuts by extraction with a mixture of ether and alcohol. Even after the most careful purification, commercial tannic acid is not a homogeneous compound but a mixture.

Pure tannic acid is a colourless amorphous substance, which dissolves readily in water and sparingly in alcohol and ether. The aqueous solution possesses a bitter astringent taste and is coloured dark blue by ferric salts, hence its use in the manufacture of ink.[1] Tannic acid is withdrawn from its aqueous solution by animal hide, the latter being " tanned " and converted into leather (see p. 466). Tannin also precipitates many alkaloids and proteins from their solutions. This reaction provides one of the most sensitive tests for proteins. The use of tannic acid as a mordant for basic dye-stuffs was introduced by W. H. Perkin. It is also employed in medicine and for the clarification of wine.

The work of E. Fischer has thrown much light on the constitution of tannins from the leaf gall of *Rhus Semialata* (Chinese tannin) and the twig gall of *Quercus infectoria* (Turkish tannin). The last details of their constitution will probably remain unsolved for some time yet, as these amorphous products appear to be inseparable mixtures of very closely related poly-galloyl-glucoses.

Fischer has also synthesised other depsides or ester compounds of glucose with phenol-carboxylic acids. Of these, *1-galloyl-β-glucose*, $C_6H_{11}O_5.O.CO.C_6H_2(OH)_3$, was identified with the *glucogallin* of Chinese rhubarb.[2] The work culminated in the synthesis of penta-*m*-digalloyl-*β*-glucose, $[(HO)_3C_6H_2.CO.O.(HO)_2C_6H_2.CO)]_5.C_6H_7O_6$, which shows a strong resemblance to Chinese tannin, of which it may possibly be the chief constituent.[3]

Turkish tannin is less homogeneous than that from Chinese galls, as it also contains a compound of ellagic acid which is readily soluble in

[1] Ordinary writing inks commonly consist of a solution containing tannic acid (or aqueous extract of gall-nuts) and ferrous sulphate, together with certain acidic substances, gum, and phenol (to prevent mouldiness). The ferrous salt of tannic acid is first formed, or the tannic acid may become hydrolysed, giving the salt of gallic acid. These salts are soluble and only feebly coloured, and the small amount of acid (HCl or H_2SO_4) present prevents the untimely precipitation of black ferric compounds. When used for writing the acidity of the ink is neutralised by the alumina present in the paper. Oxidation then occurs and a black insoluble iron precipitate, stable to light, is formed. Owing to the pale colour of the unoxidised ink it is usual to add dyes, such as soluble indigo or aniline blue, to the above mixtures. [2] *Ber.*, 1919, **52**, 818. [3] *Ber.*, 1918, **51**, 1760. P. Karrer, *Helv. Chim. Acta*, 1923, **6**, 3.

water. In this tannin the greater part of the gallic acid is united to sugar in the form of galloyl groups, because on methylation and hydrolysis with alkali only a small proportion is recovered as *m*, *p*-dimethyl-gallic acid, the greater part being obtained as trimethyl-gallic acid. The phenolic hydroxyl groups are therefore almost entirely free in Turkish tannin, and the galloyl groups must be largely present as such and not in the form of condensed groups such as digalloyl. The relative proportion of sugar to gallic acid is considerably larger than in Chinese tannin, 1 mol. glucose corresponding to about 5 or 6 mols. gallic acid.

Hamameli-tannin,[1] obtained from the bark of *Hamamelis Virginica*, crystallises well and may be regarded as homogeneous. It forms colourless needles of $[\alpha]_D^{20} = +35{\cdot}6°$ in 1·2 per cent. aqueous solution. In place of glucose it contains some other hexose combined with gallic acid in the form of an ester, as in the gallotannins. None of the phenolic groups are substituted and each galloyl residue is united through the carboxyl to a hydroxyl group of the sugar. From the degradation of hamameli-tannin by fermentation the proportion of gallic acid to hexose has been found to be 2 : 1. Analytical results agree with a di-galloyl hexose.

The discovery that ester compounds of sugar with phenolic carboxylic acids constitute a large class of tannins is of great importance in connection with plant physiology. It is of particular interest that the sugar of the plant is used in the same way as glycerol and the monohydric alcohols in the esterification of acids.

Tannigen, apparently prepared by treating tannic acid with acetic anhydride and ethyl acetate, is probably a diacetyl tannin. It is used medicinally in cases of chronic diarrhœa.

A number of other naturally occurring tannins have as yet been little investigated. These are usually named after the plant in which they occur. They all dissolve readily in water, possess a bitter taste, give a dark blue or green colour with ferric salts, are precipitated with lead acetate solution, precipitate proteins and transform animal hide into leather. Some of these compounds are glycosides of gallic or other closely related acids.

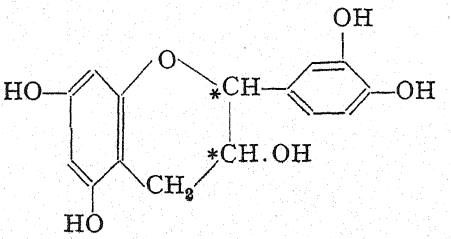
Among such substances may be mentioned *kino-tannin*, the chief constituent of kino ; *moringa-tannin* or *maclurin*, extracted from the yellow wood of *Morus tinctoria* by means of hot water ; the tannin of coffee, occurring in coffee beans and Paraguay tea ; and *oak tannin*, occurring in the bark of oak. From cinchona or Peruvian bark is obtained a tannin which is present in combination with the cinchona alkaloids. The commercially valuable *tannin of the chestnut* is related to that of the native oak : when treated with dilute mineral acids it yields ellagic acid, glucose and traces of gallic acid. Its behaviour on fermentation appears to exclude it from the class of ester tannins, to which the gallo-tannins belong, and it also shows no similarity to the catechins, since it contains no phloroglucinol, is strongly acidic and is almost insoluble in ethyl acetate.[2]

Catechins.—This group includes a number of isomeric compounds of the composition $C_{15}H_{14}O_6$ which are present in *cutch* or *catechu*, a product prepared from various plants by extraction with hot water. *Gambier catechu* is obtained from the bush *Uncaria gambier* (Malacca, Penang, Singapore) ; *Bengal* or *acacia catechu* from the wood of *Acacia*

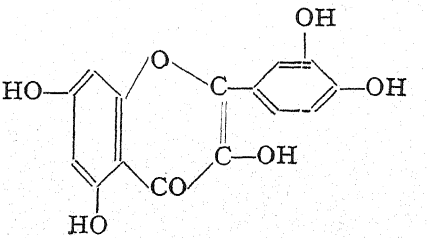
[1] K. Freudenberg, *Ber.*, 1919, **52**, 177 ; 1920, **53**, 953. *Ann.*, 1924, **440**, 5. [2] K. Freudenberg and H. Walpaski, *Ber.*, 1921, **54**, 1695.

catechu (India, Burma); *Bombay* or *areca catechu* from the fruit of the betel nut palm tree, *Areca catechu* (Asia); and *mangrove cutch* from the bark of the mangrove, *Ceriops candolleana*. The pure catechins are colourless crystalline derivatives of phloroglucinol. They form the basis of many natural tannins, and under the influence of mineral acids, enzymes or heat they readily change into amorphous tannins or tannin reds.

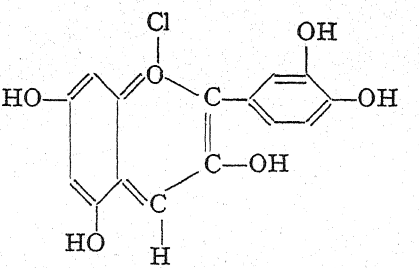
The constitution of these compounds has proved an exceedingly difficult problem, but the researches of Freudenberg, based on earlier work of Kostanecki and of A. G. Perkin, have now shown the catechins to be isomerides of the following structure I. This constitution is closely related to that of the flavone dye-stuffs [1] (*e.g.* quercetin II) and the anthocyanidins (*e.g.* cyanidin chloride III). The relationship to the natural flower pigments was proved [2] by the conversion of cyanidin chloride (p. 829) into *r-epi*catechin by reduction in alcoholic solution, using platinum black and hydrogen.



I. Catechin



II. Quercetin



III. Cyanidin chloride.

As may be seen from formula I, these compounds may exhibit *cis* and *trans* isomerism due to a different arrangement of the groups around the two C-atoms marked *. Catechin itself is believed to be of the *trans* type, and the more recently discovered *epi*catechin of the *cis* variety. In addition the two marked atoms are asymmetric, thus giving rise to optically active and racemic forms of catechin and *epi*catechin.

It appears that, owing to the crude methods in use, a certain amount of *cis-trans* isomerisation and racemisation occurs during the process of extraction. Freudenberg and Purmann [3] carefully extracted acacia heart-wood at a low temperature and found the product to consist almost

[1] Formula I for catechin and the relationship to quercetin were first suggested by A. G. Perkin and Yoshitake, *J. C. S.*, 1902, **81**, 1162; 1905, **87**, 398. [2] Freudenberg and co-workers, *Ann.*, 1925, **444**, 134. [3] *Ann.*, 1924, **437**, 274.

entirely of *l-epi*catechin and a little *r*-catechin. The technical product from this source examined by A. G. Perkin,[1] and named by him *aca*-catechin, has been found to be a mixture of stereoisomerides (*r*-catechin, together with *l*-catechin, *l-epi*catechin and *r-epi*catechin), formed apparently by the transformation of *l-epi*catechin.

A red amorphous substance known as **catechutannic acid** is present in small amounts in *Gambier catechu*, and in considerably larger quantities in the browner varieties of cutch. It is believed to be an anhydride of catechin and is a powerful tanning agent.

Cutch or catechu is also used as a dye, giving a fast brown colour on cotton. For this purpose it is employed in combination with copper sulphate followed by treatment with potassium bichromate. It is also used as a preservative for fishing nets, sailcloth, etc.

Tanning of Hides

Animal skins rapidly putrefy in the moist state, and on drying become stiff and hard. By tanning they may be converted into leather, which resists decay and remains pliable when dried. According to the materials employed, a distinction is drawn between *bark*, *mineral* and *oil tanning*. It is mainly in the first and oldest of these processes that the tannins are used.[2]

The materials used as sources of the tannins are as follows: oak bark, pine bark (Saxony, Hungary), hemlock fir (North America), larch (England), birch and willow (Russian leather, Swedish and Danish glove leather). A wood rich in tannins is *quebracho* wood, containing on the average 20 per cent. of tannin, extracts of which are imported in considerable quantities from the Argentine. Extracts from wood of the oak and chestnut, and also from various barks, are made by treatment with hot water and subsequent concentration. Such extracts are employed on a large scale.

The skins must first be prepared and rendered capable of readily absorbing the tanning liquor. Of the two main layers of which the hide consists, viz. the epidermis (outer layer) and the corium or dermis (true skin), the latter alone is required. The fresh skin is therefore hung in running water to remove blood and dirt, and the hair and epidermis loosened by treatment with lime, sulphides, or decomposing dung, which also makes the texture more open. The epidermis and hair are then removed by scraping with blunt tanners' knives.

The subsequent tanning process may be effected with tan bark, which takes a considerable time, or may be completed much more rapidly by the use of *tannin extracts*. In the former method the skins are hung in pits containing tan liquor of greater and greater concentration over a period of six to eight weeks, and are then transferred to the "layers." In these the skins are placed in layers, each being dusted over with the solid tanning material and the whole covered with strong tan liquor. The liquor is usually withdrawn and renewed several times, the length of treatment varying with the thickness of the hide from three to six months or more.

With the aid of tannin extracts, on the other hand, a skin may be completely tanned in from two to twelve weeks, according to thickness.

Certain tannin substitutes have recently come into use, such as *neradol* (a condensation product of phenol-sulphonic acid with formaldehyde), *neradol D*, and *ordoval*.

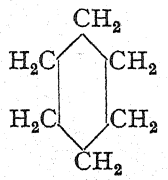
It has not yet been determined with certainty whether the tannin is deposited mechanically in the hide or enters into chemical combination with it. The changes taking place probably follow in the main the laws of colloid chemistry.

[1] *J. C. S.*, 1902, **81**, 1160; 1905, **87**, 404. [2] *Oil tanning* (for chamois leather) is effected with the aid of fish oil; in mineral tanning use is made of a solution of alum and common salt (*alum tanning*), basic chromium salts (*chrome tanning*), or iron salts. Chrome tanning has recently become a serious rival to vegetable tanning.

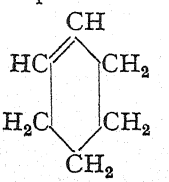
XII

Hydroaromatic Compounds

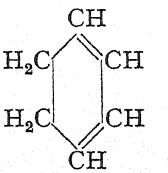
Benzene and its derivatives can take up hydrogen, without disruption of the six-membered ring, to form hydroaromatic compounds. Although the latter possess the same ring structure as the aromatic compounds, they differ from them in many points and show more resemblance to the aliphatic series. The carbon ring of hexahydrobenzene, or cyclohexane, exhibits approximately the same degree of stability as that of cyclopentane (p. 355), and these compounds and their derivatives behave in the main like the paraffins—although somewhat more reactive in consequence of their cyclic structure. On the other hand, tetrahydrobenzene and the dihydrobenzenes correspond to the olefins.



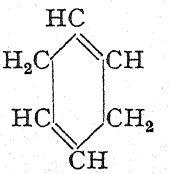
Hexahydrobenzene



Tetrahydrobenzene



$\Delta^{1:3}$-Dihydrobenzene



$\Delta^{1:4}$-Dihydrobenzene

Only one tetrahydrobenzene exists but two dihydrobenzenes are possible. Numerous cases of isomerism occur among derivatives of these hydrocarbons according to the position of the double bond or bonds, which must therefore be indicated. For this purpose the six carbon atoms of the hexagon ring are numbered and the position of a bond indicated by the Greek letter Δ, to which is attached an index number corresponding to the first atom of the doubly linked pair, as illustrated in the above formulæ.

The hydrobenzenes and their derivatives are described in the succeeding pages, a separate section being devoted to the terpenes, which are derived from reduced cymenes.

Many hydroaromatic compounds are distinguished by the ease with which they may be transformed into the corresponding aromatic substances.

I.—HYDROCARBONS, ALCOHOLS, KETONES, ALDEHYDES AND ACIDS OF THE CYCLOHEXANE SERIES

Occurrence.—Hydrocarbons of the cyclohexane series are present in considerable quantities in Caucasian petroleum. The mixture of hydrocarbons known as **naphthenes**, obtained by fractionating the petroleum, consists mainly of cyclopentanes and cyclohexanes.[1]

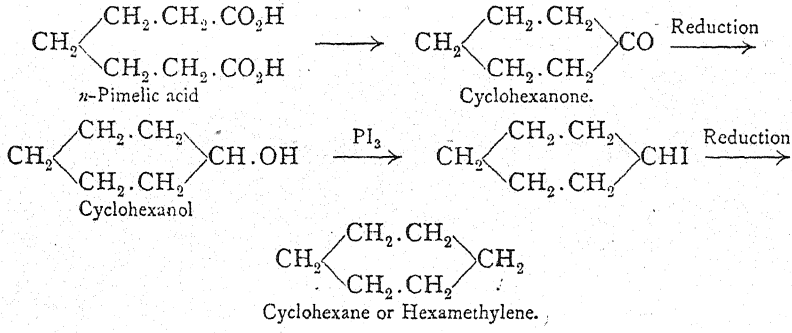
Formation.—A number of methods of synthesising cyclohexane derivatives have already been described and these may be briefly summarised:

Many have been prepared by reduction of the corresponding benzene

[1] For the origin of naphthenes and naphthenic acids, see O. Aschan, *Ann.*, 1902, **324**, 1. For the constitution of *naphthenic acids* see also N. Zelinsky and E. Pokrowskaja, *Ber.*, 1924, **57**, 51.

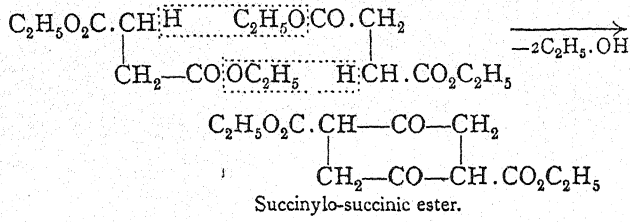
compounds, recently with the use of metals of the platinum group as catalysts. The method of Sabatier and Senderens (passing the vapour of the substance, mixed with hydrogen, over heated, finely-divided nickel) may also be satisfactorily employed for this purpose.[1]

In other methods aliphatic compounds form the starting-point. Cyclic ketones, as already explained, are produced by distilling the calcium salts of dibasic acids, cyclohexanone, for example, being obtained from calcium pimelate. Cyclohexane itself was first synthesised by Baeyer in the following stages :



Later it was also prepared from hexamethylene dibromide, by reduction with sodium.

An interesting reaction, already mentioned on p. 275 (see also Ester Condensations, p. 256), consists in the conversion of diethyl succinate into *succinylo-succinic ester* by treatment with metallic sodium. This substance serves for the preparation of further cyclohexane derivatives.



Finally, it may be noted that the Grignard reaction has also been applied with success to synthesis in the cyclohexane series.

By the distillation of coal *in vacuo* A. Pictet and M. Bouvier [2] obtained a tar from which two hydrocarbons, $C_{10}H_{20}$ and $C_{11}H_{22}$, were isolated. They also isolated the same hydrocarbons from Canadian petroleum, thus establishing an experimental connection between these two natural products. The hydrocarbon $C_{10}H_{20}$ from the above vacuum tar boils at 172° and 174°, and is most probably *hexahydrodurene* (1 : 2 : 4 : 5-tetramethyl-cyclohexane), while the compound $C_{11}H_{22}$, b.p. 189° to 191°, is possibly the *hexahydride of pentamethylbenzene.*

[1] Sabatier and Mailhe, *C.*, 1906, I, 1248. Sabatier, *Ber.*, 1911, 44, 1984. Zelinsky, *Ber.*, 1911, 44, 2779, 3121 ; 1925, 58, 1298. [2] *Ber.*, 1913, 46, 3342.

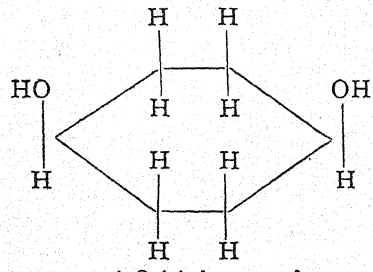
Cyclohexane and its Derivatives

Cyclohexane, *hexahydrobenzene, hexamethylene, naphthene,* C_6H_{12}, is formed by the above reactions and may be obtained from pure benzene by reduction with platinum and hydrogen.[1] It is an important constituent of Caucasian petroleum and is a colourless liquid, b.p. 81° (corr.) and m.p. 6·4°, with a smell like benzine. A characteristic property is the ease with which it is oxidised to adipic acid by nitric acid. *Benzene hexachloride,* $C_6H_6Cl_6$, a chloro-derivative of cyclohexane, is formed by leading chlorine into benzene, and exists in two modifications (m.p. 157° and 310°). *Monochlorocyclohexane* is readily prepared by the action of chlorine on cyclohexane. Unlike alkyl halides, these monochloro- and bromo-derivatives do not yield alcohols when treated with alkalis, but form **tetrahydro-benzene,** C_6H_{10}. The latter is a colourless liquid boiling at 83° to 84° (743 mm.). Amino-derivatives of hexahydrobenzene resemble aliphatic amines in their behaviour.

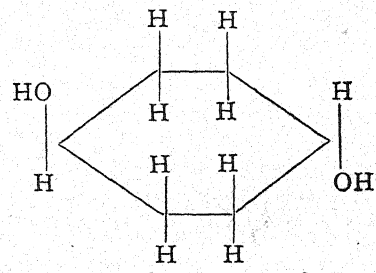
Cyclohexanol, *hexahydrophenol,* $C_6H_{11}.OH$, is produced in good yield by leading a mixture of phenol vapour and hydrogen over finely-divided nickel at 140° to 160°. It is a colourless liquid, b.p. 160·5°, which solidifies at a low temperature to a mass of melting-point 20°. With hydrobromic acid it yields the above-mentioned *monobromocyclohexane,* b.p. 162°, and with hydriodic acid *mono-iodo-cyclohexane,* b.p. 180°. When hexahydrophenol is heated with oxalic acid, water is eliminated and tetrahydrobenzene formed.

Quinitol, *cyclohexane-*1:4*-diol,* (hexahydro - hydroquinone), was obtained by Baeyer, by reducing cyclohexane-1:4-dione (see p. 471) with sodium amalgam. It exists in two stereoisomeric forms.

This type of isomerism is similar to that described under fumaric and maleic acids (p. 48), the ring structure hindering free rotation of the carbon atoms in the same manner as the double bond of the ethylene series. Polymethylene derivatives thus exhibit stereosiomerism due to the different spatial positions of the atoms with reference to the plane of the ring, exactly analogous to the geometrical isomerism of ethylene compounds, in which the atoms occupy different positions in space as referred to the plane of the double bond. Theory therefore predicts that each disubstitution product of a polymethylene should exist in two



cis-Quinitol, m.p. 102°



trans-Quinitol, m.p. 139°.

[1] Willstätter and Hatt, *Ber.*, 1912, 45, 1471. Skita, *Ber.*, 1912, 45, 3312.

stereoisomeric forms, according as the substituent atoms or groups lie on the same or on opposite sides of the plane of the ring. In agreement with this, two isomeric quinitols are known, corresponding to the formulæ on p. 469.

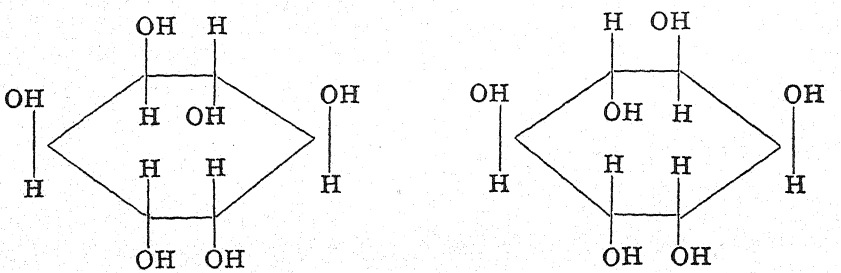
These differ in their configuration in such a way that in *cis*-quinitol the hydroxyl groups lie on the same side, and in *trans*-quinitol on opposite sides of the plane of the ring.[1]

Quercitol, *cyclohexane-pentol,* $C_6H_7(OH)_5$, is found in an optically active form in acorns (hence *acorn sugar*). It melts at 235°.

Inositol, *cyclohexane-hexol,* $C_6H_6(OH)_6$, is known in an inactive mesoform, a racemic and two optically active forms. It is found in the muscles of the heart, in liver and in various plants. It has the same empirical formula as the hexoses, which it also resembles in having a sweet taste.

The active inositols (*d*- and *l*-) are of interest as being the first known optically active compounds containing no asymmetric atom.[2]

Their configurations have been represented by Bouveault in the following manner:



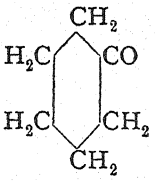
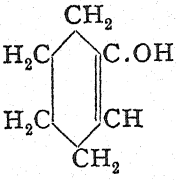
since of the nine theoretically possible isomerides of hexahydroxy-cyclohexane only these two mirror-image structures are without a plane of symmetry.

Cyclohexanone, ketohexamethylene, is formed by heating the calcium salt of *n*-pimelic acid [3] (see p. 276), and can be prepared by oxidation of the corresponding alcohol cyclohexanol. It is an oil, b.p. 155°, with a smell of peppermint. On reduction it yields cyclohexanol, and on oxidation with nitric acid gives adipic acid.

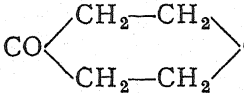
Cyclohexanone is a tautomeric compound and may react either as a ketone or as a hydrogenated phenol (Δ^1-tetrahydro-phenol, see p. 471).

As a ketone it unites with hydroxylamine and sodium bisulphite, and as a phenol it may be acetylated by boiling with acetic anhydride to form the acetyl ester of Δ^1-tetrahydro-phenol, b.p. 180° to 181°.

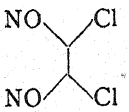
[1] Numerous other stereoisomeric polymethylene derivatives are known, particularly among the carboxylic acids. [2] Other examples are 1-methyl-cyclohexylidene-4-acetic acid (Perkin, jun., *J. C. S.*, 1908, **93**, 1943; Perkin and Pope, 1909, **95**, 1789), and derivatives of diphenyl and naphthalene described on p. 41. [3] Alkyl keto-hexamethylenes may be obtained in a similar manner from alkyl pimelic acids, Zelinsky and Generosow, *Ber.*, 1896, **29**, 729.

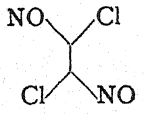



***p*-Diketo-hexamethylene**, *cyclohexane*-1:4-*dione*, *tetrahydro-quinone*,



is obtained from succinylo-succinic ester (p. 468) by hydrolysis and elimination of carbon dioxide. It melts at 78°, and on reduction yields quinitol. *p*-Diketo-hexamethylene forms a dioxime, which in the presence of pyridine reacts with bromine in much the same manner as acetoxime (p. 163) to give *p*-dibromo-dinitroso-hexamethylene, $ON.CBr(CH_2.CH_2)_2.CBr.NO$. With chlorine the corresponding chloro-nitroso compound is formed. Both of these halogen derivatives occur in two stereoisomeric forms, as illustrated in the following formulæ [1]:


cis-Form


trans-Form.

Up to the present few aldehydes of this series are known. **Hexahydro-benzaldehyde**, $C_6H_{11}.CHO$, b.p. 159°, is obtained by the oxidation of *hexahydro-benzyl alcohol*, $C_6H_{11}.CH_2OH$. **Hexahydro-*m*-toluic aldehyde**, $CH_3.C_6H_{10}.CHO$, has been prepared by treating orthoformic ester with methylcyclohexyl magnesium bromide.[2] It is a liquid of strong odour, b.p. 176° to 178°.

Hydro-aromatic carboxylic acids resemble aliphatic acids in their properties. The following compounds of this type may be mentioned.

Hexahydro-benzoic acid, $C_6H_{11}.COOH$, can be obtained by the reduction of benzoic acid, by the action of carbon dioxide on cyclohexyl magnesium iodide,[3] and by a number of other methods. It crystallises in prisms, melts at 30° to 31°, boils at 232°, and has a rancid odour. Numerous homologues of this acid are known, which are probably isomeric with the natural *naphthenic acids* occurring in Caucasian petroleum.

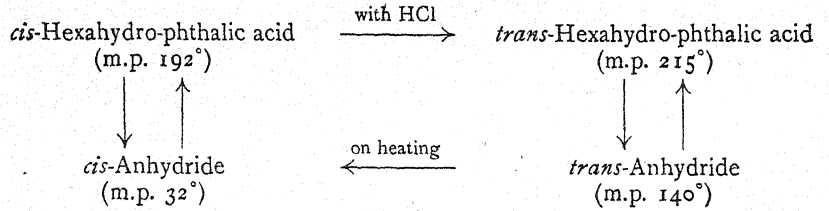
Quinic acid, *tetrahydroxy-hexahydro-benzoic acid*, $(HO)_4C_6H_7.COOH$, is present in cinchona bark, coffee beans, sugar beet and other sources. The acid prepared from cinchona bark is optically active and melts at 162°. It is also known in an inactive form. On oxidation it is converted into quinone, and when heated with hydriodic acid gives

[1] Piloty and Steinbock, *Ber.*, 1902, **35**, 3101. [2] Tschitschibabin, *Ber.*, 1904, **37**, 850.
[3] Zelinsky, *Ber.*, 1902, **35**, 2687.

benzoic acid. With benzoyl chloride it yields *dibenzoylhydroquinone*, $C_6H_4(O.COC_6H_5)_2$, m.p. 199°.

The **hydro-phthalic acids** were carefully examined by Baeyer[1] in an attempt to determine the constitution of benzene. Although unsuccessful in this respect, these arduous investigations brought to light the existence of a number of isomerides, since both structural isomerism and stereo-isomerism may occur among these compounds.

Thus the reduction of phthalic acid has led to the isolation of eleven different *dihydro-phthalic acids*, $C_6H_6(COOH)_2$, four *tetrahydro-phthalic acids*, $C_6H_8(COOH)_2$, and two *hexahydro-phthalic acids*, $C_6H_{10}(COOH)_2$. Several hydro-derivatives of terephthalic and isophthalic acids are also known. We are dealing here with the same type of geometrical isomerism as was outlined in connection with quinitol (p. 469), i.e. *cis-trans* isomerism. In their interconversions the isomerides recall the behaviour of ethylene derivatives, as is seen in the case of the hexahydro-phthalic acids.



II.—TERPENES AND CAMPHORS[2]

Terpenes are cyclic hydrocarbons of the formula $(C_5H_8)_n$, and occur widely distributed in nature. They are the chief constituents of the "essential oils" obtained by distilling with steam the sap and tissues of certain plants—particularly those of the coniferous and citrus families. Essential oils or ethereal oils prepared in this way are used in the production of perfumes and in pharmacy. Accompanying the terpenes are also found oxygen derivatives of the terpenes (alcohols and ketones), which are classed under the name of *camphors*, and certain closely related open-chain alcohols and aldehydes known as *olefinic terpenes* (*cf.* p. 155). Terpenes and essential oils have been the subject of many careful and elaborate investigations from 1884 onwards, more especially at the hands of O. Wallach.

Hydrocarbons of this group are generally subdivided into *terpenes*, $C_{10}H_{16}$, *sesquiterpenes*, $C_{15}H_{24}$, *diterpenes*, $C_{20}H_{32}$, *triterpenes* and so on. The different classes are readily distinguished by the marked differences in boiling-point.

[1] The results are summarised in *Ber.*, 1890, **23**, 1272, and *Ann.*, 1892, **269**, 176. [2] Compare O. Wallach, *Terpene und Campher* (Leipzig, 1909). *Natural Terpenes*, J. W. Baker (Methuen, 1930). *The Terpenes*, J. L. Simonsen (Camb. Univ. Press, 1931).

The terpenes, $C_{10}H_{16}$, are all unsaturated hydrocarbons containing either one or two ethylene bonds in the molecule, according to which they are again divided as follows :—

1. **Monocyclic terpenes,** containing two double bonds. These are dihydro-cymenes, and may therefore be regarded as partially reduced benzene derivatives. Included in this class are limonene (dipentene), sylvestrene, terpinene and terpinolene. Owing to the presence of two double bonds they are capable of adding on two or four monovalent atoms or groups.

2. **Dicyclic terpenes,** containing one double bond in the molecule. These are built up of two ring systems, *e.g.* a combination of a cyclohexane with a cyclobutane ring. Compounds of this type are pinene, camphene and fenchene, each of which can unite with two monovalent atoms or groups.

Camphors and other terpene derivatives can be classified in a similar manner.

According to recent work,[1] the **sesquiterpenes** are related to naphthalene in the same way as the terpenes to benzene. Comparatively little is known of the chemistry of this group.

Of the above compounds only the terpenes proper can be treated with any detail in these pages.

Properties and Chemical Behaviour.—Camphene is a solid at ordinary temperatures, but with this exception the terpenes are colourless, strongly-refracting liquids, which boil between 150° and 180°, are insoluble in water and volatilise readily with steam. They are characterised by a pleasant smell, and many of them are optically active.

Their nature as unsaturated compounds is shown by their addition reactions and tendency to polymerise. They unite with chlorine, bromine,[2] and hydrogen halides to form halogen-substituted compounds, which are of interest as being intermediate products in the transformation of terpenes into terpene alcohols. Further, many terpenes add on N_2O_3, N_2O_4, NOCl and NOBr to yield nitrosites, nitrosates, nitroso-chlorides and nitroso-bromides (see p. 120).

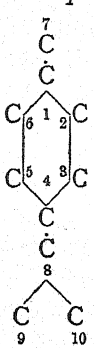
A number of the terpenes are labile, readily isomerising under the influence of acids, for example, into a more stable form.

Another point of interest is the behaviour of the terpenes on oxidation. In many cases this is effected even by atmospheric oxygen, with the production of resins. The action of mild oxidising agents (iodine, dilute nitric acid) frequently leads to the formation of benzene derivatives, or breaks down the terpenes to known aliphatic compounds. This process is often used in determining their structure. Energetic oxidising agents, such as concentrated nitric acid, generally produce complete resinification.

[1] See Ruzicka and co-workers, *Helv. Chim. Acta*, 1921, 4, 505; 1922, 5, 345, 369; 1924, 7, 84. [2] Baeyer and Villiger have made use of exhaustive bromination as a means of determining the structure of the carbon framework of many terpenes.

Monocyclic Terpenes and Camphors

Nomenclature.—The majority of the monocyclic terpenes are derived from *p*-cymene, and a few from *m*-cymene. Following a suggestion of Baeyer, the structure of these compounds is expressed by reference to the saturated parent hydrocarbon, *e.g.* hexahydro-cymene, the carbon atoms of which are numbered as in the annexed formula. The position of the double bond is indicated in the usual way (see p. 467), a double bond between the atoms 2 and 3 being shown by Δ^2.

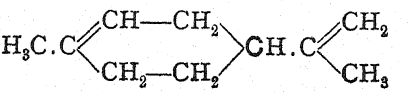


Hexahydro-cymene, $C_{10}H_{20}$, commonly known as *menthane*, is not found in nature but may be prepared by reducing *p*-cymene with hydrogen and finely-divided nickel. It boils at 170°.

Tetrahydro-cymenes are therefore described as *menthenes*, and dihydro-cymenes as *menthadienes*.

Terpenes

Limonene, $\Delta^{1:8}$-*menthadiene*,



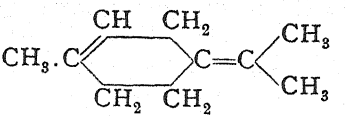
exists in dextro-, lævo- and inactive forms, as would be expected from the presence of an asymmetric atom in the molecule.[1]

d-**Limonene**, also known as carvene, citrene or hesperidene, is the chief constituent of the oil of orange rind, dill oil and oil of cumin. It occurs together with pinene in oil of lemons. *l*-**Limonene** is found with *l*-pinene in pine-needle oil; it may be prepared from carvone or from perillaldehyde.[2] Both forms of limonene are liquids of boiling-point 175°, with a strong smell of lemons. They yield crystalline tetrabromides, $C_{10}H_{16}Br_4$, m.p. 104° to 105°, which are also distinguished by rotations of opposite sign. Both limonenes unite with nitrosyl chloride,[3] each forming two compounds differing in specific rotation. On treatment with alkali these part with hydrochloric acid and are transformed into the oxime of carvone.

dl-**Limonene, dipentene**, *cinene*, is produced by mixing equal amounts of *d*- and *l*-limonenes, and is found associated with cineol, $C_{10}H_{18}O$, in oleum cinae. It is formed by the elimination of water from terpineol, and from pinene or camphene by heating at 250° to 270°. It smells of lemons, boils at 175°, and its tetrabromide melts at 124°. Among its derivatives are terpineol, $C_{10}H_{17}OH$, terpin, $C_{10}H_{18}(OH)_2$, and cineol, $C_{10}H_{18}O$.

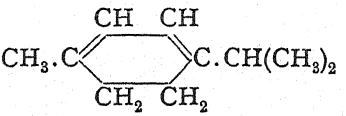
[1] For the constitution see F. W. Semmler, *Ber.*, 1900, **33**, 1457. [2] Semmler and Zaar, *Ber.*, 1911, **44**, 52. [3] Tilden and Shenstone, *J. C. S.*, 1875, **13**, 514.

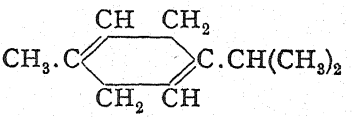
Terpinolene, $\Delta^{1:4(8)}$-*menthadiene*,



is obtained when terpineol (p. 477) is heated for a short time with oxalic acid solution. It boils at 183° to 185°, and on further treatment with acids readily yields terpinene.

Terpinene, $\Delta^{1:3}$-*dihydro-cymene* and $\Delta^{1:4}$-*dihydro-cymene*,[1]





is present in cardamom oil and is optically inactive. It smells like cymene and boils at 179° to 181°. Terpinene is formed when dipentene or phellandrene is boiled with dilute sulphuric acid, and is distinguished by its stability towards mineral acids. Hence it is also obtained when terpin hydrate, cineol, terpineol or dihydro-carveol is heated with dilute sulphuric acid. Terpinene is conveniently prepared by shaking pinene (oil of turpentine) with concentrated sulphuric acid. It forms a nitrosite of melting-point 155°, but does not give definite addition products with bromine or hydrogen halides. Ordinary terpinene consists mainly of $\Delta^{1:3}$-dihydro-cymene and contains also some $\Delta^{1:4}$-dihydro-cymene.

Sylvestrene,[2] $C_{10}H_{16}$, b.p. 176°, is the limonene of the *m*-cymene series, and has been prepared from Swedish and Russian turpentines. Simonsen and Rao have shown that it does not occur naturally in these sources but is formed from the carene present by secondary changes due to the treatment of the oils with hydrogen chloride (see p. 481).

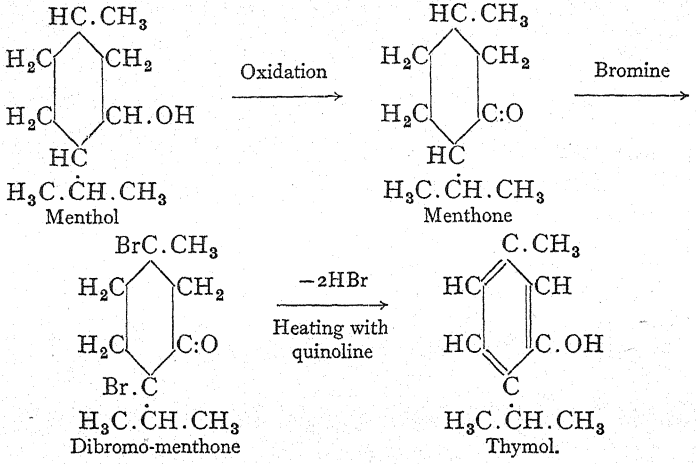
Phellandrene, $C_{10}H_{16}$, was first isolated from water-fennel (*Phellandrium aquaticum*) from which it takes its name. It also occurs in other ethereal oils and exists in *d*- and *l*-forms, neither of which has yet been obtained in the pure state. With acids it very readily undergoes change.

Alcohols and Ketones

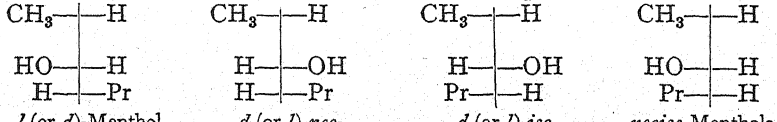
***l*-Menthol**, 3-*menthanol*, is the odorous and chief constituent of oil of peppermint, from which it may be separated in the solid state by cooling. It melts at 43°, boils at 213° and is employed as an antiseptic and anæsthetic. On reduction it yields hexahydro-cymene. When oxidised with potassium bichromate in acid solution it is converted into the corresponding ketone, **menthone**, b.p. 207°, which also occurs in oil of peppermint and other essential oils. The constitution of menthol and

[1] Harries and Majima, *Ber.*, 1908, **41**, 2516. Wallach, *Ann.*, 1908, **362**, 293. Semmler, *Ber.*, 1908, **41**, 4474. F. Richter and Wolff, *Ber.*, 1927, **60**, 477. [2] For synthesis see Perkin, *Proc. Chem. Soc.*, 1910, **26**, 97.

menthone is shown by the conversion of the latter into thymol as follows [1]:

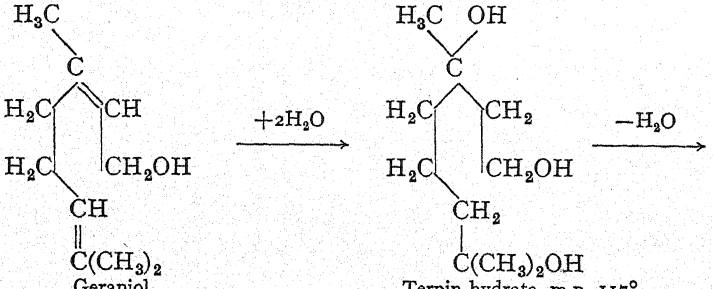


Owing to the presence of three asymmetric carbon atoms in the molecule, various isomeric forms of menthol are possible. The relative configurations of these compounds have been established by Read [2] (see p. 478). In the following formulæ Pr = C_3H_7. The elimination of water to form a Δ^3-menthene occurs most readily with *neo-* and *neoiso-*menthols, in which H and OH are in the *trans* position to one another.

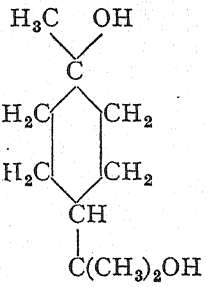


l (or *d*)-Menthol, m.p. 43° | *d* (or *l*)-*neo*-Menthol, an oil | *d* (or *l*)-*iso*-Menthol, m.p. 81° | *neoiso*-Menthols.

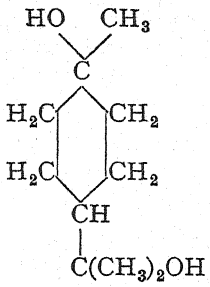
Terpin, 1:8-*menthane-diol*, $C_{10}H_{20}O_2$, exists in two stereoisomeric (*cis-* and *trans-*) forms. A crystalline hydrate of terpin, known as *terpin hydrate*, is produced when pinene or dipentene is allowed to stand for some time at the ordinary temperature in contact with dilute mineral acids. Terpin hydrate is also formed from geraniol by treatment with dilute sulphuric acid. On prolonged heating at 100° it yields *cis*-terpin.



[1] Beckmann and Eickelberg, *Ber.*, 1896, **29**, 418; also Jünger and Klages, *Ber.*, 1896, **29**, 314. For syntheses of menthol see Perkin, jun., *Proc. Chem. Soc.*, 1905, **21**, 255; Kötz and Hesse, *Ann.*, 1905, **342**, 306. For a synthesis of optically active menthone see Kötz and Schwarz, *Ann.*, 1907, **357**, 209. [2] J. Read and W. J. Grubb, *J. C. S.*, **1934**, 1779.

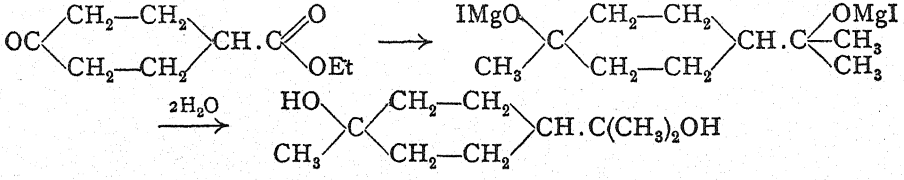


cis-Terpin
m.p. 104°, b.p. 258°

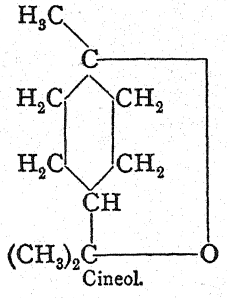


trans-Terpin
m.p. 156-158°, b.p. 236-265°.

Perkin and Kay [1] have synthesised terpin by treating cyclohexanone-4-carboxylic ester with excess of methyl magnesium iodide, and have thus confirmed its constitution.

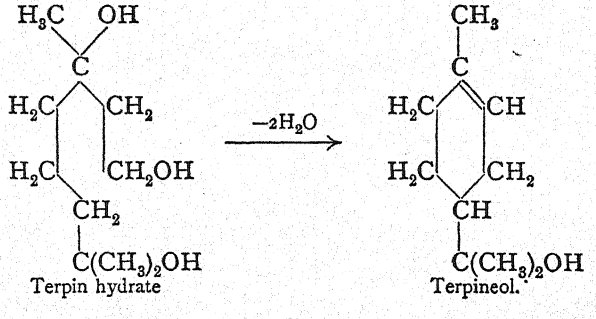


Cineol, of the annexed formula, is an inner anhydride of terpin, and occurs in many ethereal oils, such as oil of eucalyptus, wormseed oil and rosemary oil. It is a liquid of boiling-point 176°, with a smell of camphor. When treated with hydrochloric acid in glacial acetic acid solution, it is converted into dipentene dihydrochloride, $C_{10}H_{18}Cl_2$.



Cineol.

Terpineol, Δ^1-*menthen*-8-*ol*, is a solid, m.p. 35°, and b.p. 219°. It is obtained from terpin hydrate by treating it under certain conditions with dilute sulphuric acid, when two molecules of water are removed as follows :—



Terpin hydrate

Terpineol.

Terpineol [2] is present in a number of essential oils and has an odour of lilac. Hence it is used in the manufacture of perfumes. When heated

[1] *J. C. S.*, 1907, **91**, 372. [2] For synthesis, see Perkin, *J. C. S.*, 1904, **85**, 654; 1908, **93**, 1871.

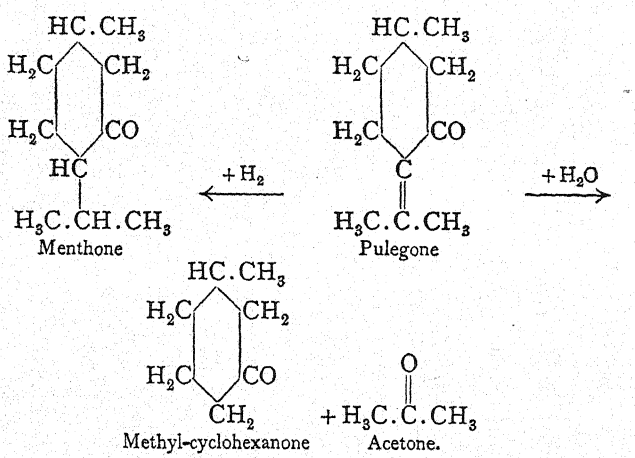
with potassium bisulphate it yields dipentene, and with oxalic acid, terpinolene. Carvacrol and carvone (see below) may be prepared from the nitrosochloride of terpineol.

Among the ketones of this group are **menthone**, already described on p. 475, piperitone, pulegone and carvone. Buchu-camphor is an example of a ketonic alcohol.

Piperitone, Δ^{1}-*menthen*-3-*one*, is an unsaturated ketone found in the *l*-form in a number of eucalyptus oils (H. G. Smith), especially in that of the Broad-leaved Peppermint (*E. Dives*). More recently a *d*-piperitone has been isolated by Simonsen from the essential oil of a Himalayan grass, *Andropogon Jwarancusa*. Piperitone has been carefully investigated by Read and his co-workers and in his hands has proved of great value in establishing the configurations of the menthones, menthols [1] and menthylamines. On hydrogenation it yields a mixture of menthone and isomenthone.

Pulegone, $\Delta^{4(8)}$-*menthen*-3-*one*, b.p. 221°, is present in oil of penny-royal. The keto-group occupies a similar position to that in menthone, into which compound pulegone may be converted by hydrogenation. When superheated with formic acid or water, pulegone is hydrolysed to 3-methyl-cyclohexanone and acetone, from which its constitution is deduced.[2] On the other hand, by the condensation of methyl-cyclo-hexanone with acetone, an isomeride of pulegone is obtained.[3]

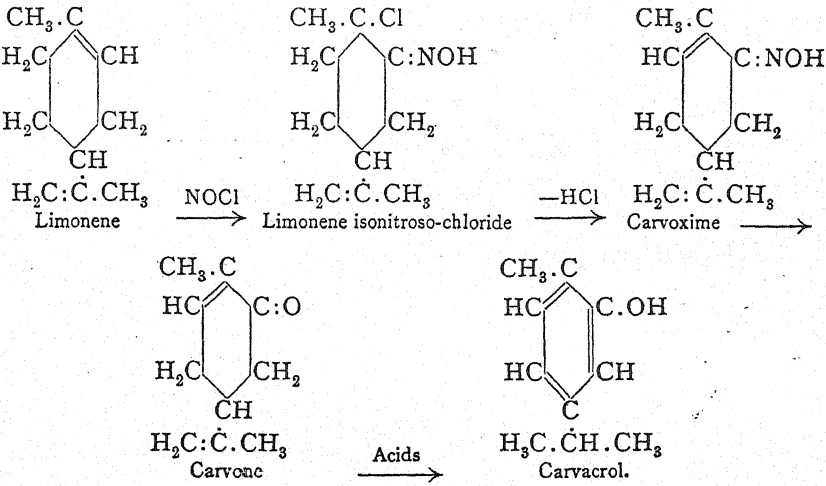
Pulegone reacts with hydroxylamine in the normal manner to form an oxime; it also yields an addition product in which hydroxylamine is attached to the unsaturated linking, the group C=C being converted into CH—C.NHOH.



Carvone, $\Delta^{6:8}$-*menthadiene*-2-*one*, formerly known as carvol, exists like limonene in *d*-, *l*- and *r*-modifications. *d*-Carvone is the odorous and chief constituent of carraway oil. It melts at 62°, and boils at 230°. It readily isomerises into carvacrol, the hydroxyl group of which has

[1] See p. 476. [2] Wallach, *Ber.*, 1899, **32**, 3338. [3] Wallach, *Ann.*, 1898, **300**, 267.

been shown to occupy the 2-position. This must also be the position of the carbonyl group of carvone. The double bond may be located from the close relationship existing between carvone and limonene, and has been established with certainty by the oxidative degradation of carvone.



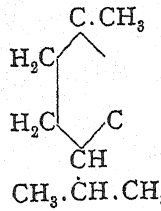
Carvone on reduction gives dihydro-carveol, and finally tetrahydro-carveol or *carvomenthol.*

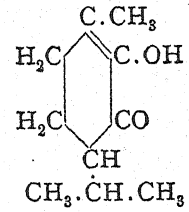
Under the influence of strong aqueous acids carvone adds on the elements of water to the double bond in the side chain to form a carvone hydrate (hydroxy-dihydrocarvone). At the same time part of the carvone is converted into carvacrol.

Diosphenol, *Buchu-camphor,* Δ^1-*menthen-2-ol-3-one,* $C_{10}H_{16}O_2$, is prepared from an essential oil obtained from various kinds of the genus *Barosina* found in South Africa. It boils at 109° to 110° under 10 mm. pressure, and melts at 83° to 84°. The constitution of this substance has been established by Semmler and McKenzie.[1] One of the two oxygen atoms is contained in an alcoholic hydroxyl group, since the compound yields an acetate and a benzoate. The second is a ketonic oxygen atom, as diosphenol forms a normal oxime. Hence the substance is a ketonic alcohol. It has also been shown to be monocyclic and unsaturated. Oxidation with ozone leads to the production of α-isopropyl-γ-acetyl-*n*-butyric acid, thus proving the structure of that part of the molecule shown in I, p. 480. The arrangement of the remaining atoms is deduced from the reduction of diosphenol to the glycol, $C_{10}H_{20}O_2$, which on oxidation yields α-isopropyl-α^1-methyl-adipic acid, thus showing the presence of a six-membered ring with methyl and isopropyl groups in the para-position to one another. The disposition of the ketonic and hydroxyl groups is now obvious. Further, it follows that the double bond must be attached

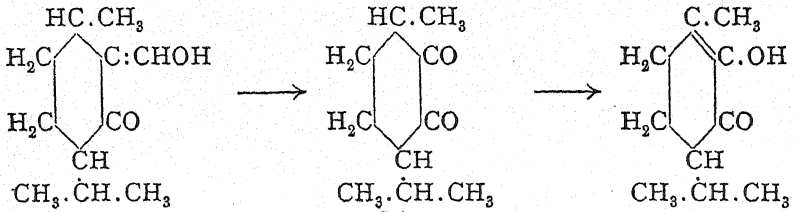
[1] *Ber.*, 1906, **39**, 1158. See also Wallach and Weissenborn, *Ann.*, 1924, **437**, 148.

to the carbon atom linked to the methyl group, the position 2 : 3 being impossible. Diosphenol therefore possesses the structure II.

I. 

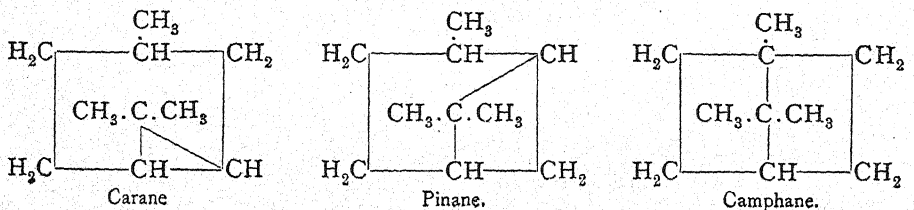
II. 

The *synthesis of diosphenol* has been effected by Semmler and McKenzie (*loc. cit.*), starting with hydroxymethylene-menthone and oxidising this to the diketone, $C_{10}H_{16}O_2$. The latter may then be transformed in various ways, *e.g.* with acids or alkalis, into diosphenol.



Dicyclic Terpenes and Camphors

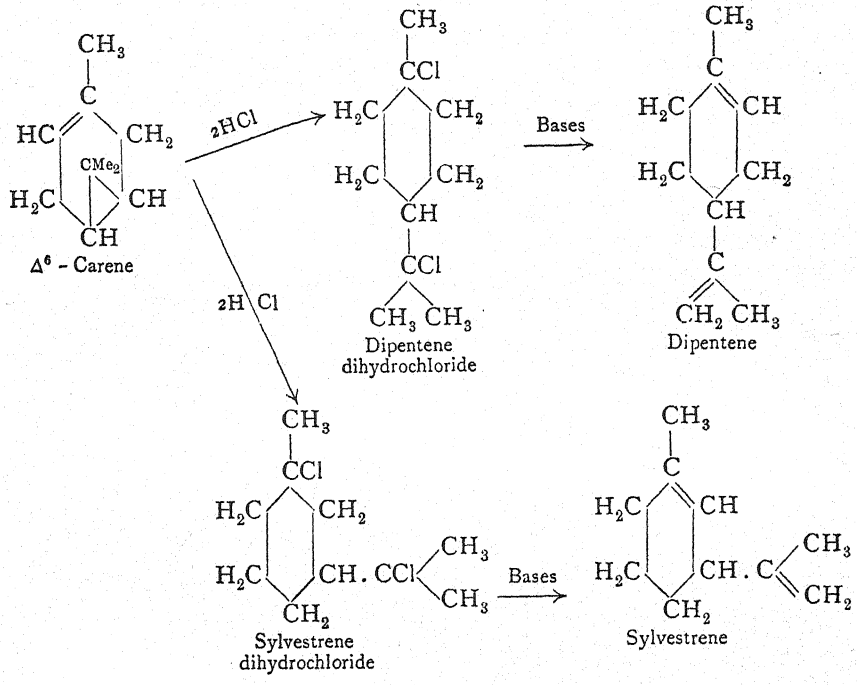
The most important member of this class is ordinary or Japanese camphor. Before discussing this compound in detail, however, the parent hydrocarbons of the alcohols and ketones will be considered. Just as many of the monocyclic terpenes may be traced back to the saturated hydrocarbon menthane, the dicyclic terpenes and their derivatives may be referred, according to the type of " bridged-ring " present, to one of the three saturated hydrocarbons, carane, pinane and camphane.



Dicyclic Terpenes

Carenes probably occur more widely in nature than was formerly supposed, but during the purification of the essential oils with hydrogen chloride they become transformed into dipentene dihydrochloride and

sylvestrene dihydrochloride by the opening of the cyclopropane ring (*Simonsen* [1]).



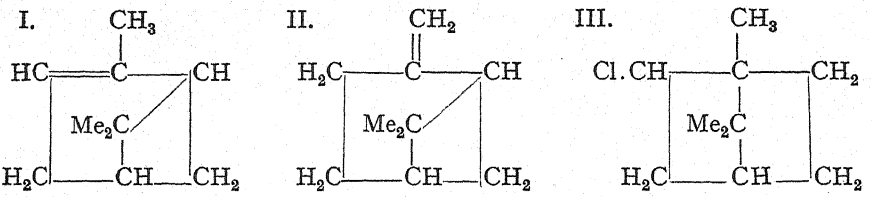
α-Pinene (I, p. 482) is a common constituent of many ethereal oils, and is especially abundant in the *turpentine oils* [2] obtained by distilling the resinous exudations of pines and firs. Associated with it is found an isomeride, **β-pinene** or **nopinene** (II). Although these compounds differ in the position of the double bond, it is not possible to distinguish between them by means of simple addition reactions, because in many cases they yield the same products. With hydrogen chloride, for example, each pinene gives the hydrochloride (III), and in the presence of dilute sulphuric acid each is converted into the same terpin. Indication of a difference in structure is furnished by their behaviour on oxidation with potassium

[1] B. S. Rao and J. L. Simonsen, *J. C. S.*, 1922, **121**, 2294; 1925, **127**, 2494. [2] Turpentine resin exudes in considerable quantities from firs, pines and other conifers when incisions are made in the bark of the tree. By distillation in steam the resin is separated into volatile turpentine oil and non-volatile colophonium (*rosin*). Turpentine oil of commerce is a colourless liquid of sp. gr. 0·85 to 0·91 and is not a homogeneous product; it boils over a range of about 155° to 165°. The oils obtained from different countries—French, Russian, American, Venetian, etc.—show varying optical rotatory power. American oil of turpentine is usually of $[\alpha]_D = +14°$, whereas French oil is of $-30°$ to $-40°$. Turpentine is an excellent solvent for resins and is largely used in the preparation of varnishes and lacquers. The United States produces yearly immense quantities of turpentine and rosin. Oil of turpentine absorbs oxygen in air, becoming thick and finally resinifying: the absorbed oxygen is thereby activated (Engler and Weissberg, *Ber.*, 1898, **31**, 3046).

Rosin consists of various modifications of the *anhydrides of sylvic acid* (*abietic acid*, $C_{20}H_{30}O_2$) and is extensively employed in the manufacture of varnishes, rosin soaps, rosin oils, and for sizing paper, etc.

permanganate, when α-pinene yields *pinonic acid* and nopinene gives *nopinic acid*. Under certain conditions α-pinene is oxidised much more readily than nopinene by mercuric acetate. β-Pinene also forms mercury addition compounds which are readily isolated.[1]

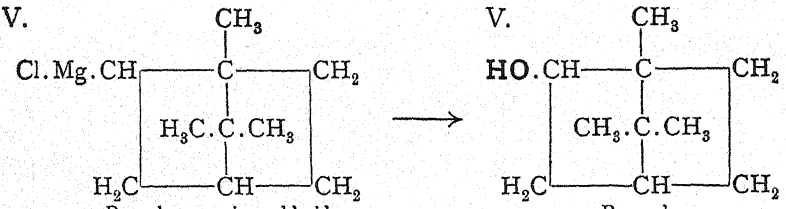
I. II. III.



Pinene combines with two atoms of chlorine or bromine to form compounds which on being heated break up into hydrogen halide and *p*-cymene. When dry hydrochloric acid gas is led into well-cooled pinene, the pinene hydrochloride first formed isomerises with great rapidity into *bornyl chloride* (III), which separates out as a crystalline mass of melting-point 131° to 132°. Owing to its close resemblance to camphor in smell and appearance, this substance is sometimes known as "artificial camphor." In its formation not only has addition of hydrochloric acid taken place, but the "pinane bridge" has simultaneously been changed into the "camphane bridge."

This is confirmed by the fact that when the magnesium compound of the hydrochloride is treated with oxygen, and the resulting product, $C_{10}H_{17}OMgCl$, decomposed with dilute acids, an almost theoretical yield of borneol (see V) is obtained.[2]

IV. V.



Bornyl magnesium chloride Borneol.

The presence of a tetramethylene ring in pinene is supported by the constitution of its oxidation products, pinonic acid and pinic acid, as well as by its synthesis.[3] When heated, pinene yields dipentene (together with isoprene, etc.). Other changes are shown in the table on p. 491.

Pinene exists in optically active forms. *d*-Pinene can be isolated by the fractional distillation of American oil of turpentine, and *l*-pinene from French turpentine. An inactive pinene is obtained by the action of aniline on active pinene nitroso-chloride, m.p. 103° (obtained from nitrosyl chloride and pinene [4]), when the nitrosyl chloride is again removed.

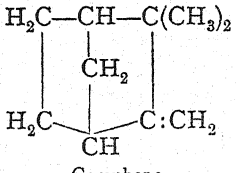
Camphene, $C_{10}H_{16}$, is a solid terpene found as the *d*-form in ginger,

[1] J. Gasopoulos, *Ber.*, 1926, **59**, 2184. [2] A. Hesse, *Ber.*, 1906, **39**, 1127. J. Houben, *Ber.*, 1905, **38**, 3801; **39**, 1700. [3] Ruzicka and Trebler, *Helv. Chim. Acta*, 1921, **4**, 666. [4] In the preparation of pinene nitrosochloride, a product of higher melting-point is obtained when alcoholic hydrochloric acid is used in place of concentrated aqueous acid. Ruzicka and Trebler, *Helv. Chim. Acta*, 1920, **3**, 756.

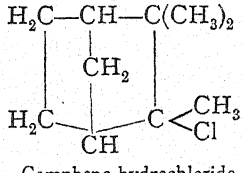
rosemary and spike oils, and as the *l*-form in citronella and valerian oils. It is produced from bornyl chloride by removing hydrogen chloride with sodium acetate and glacial acetic acid at 200°, or by heating with potassium cresolate. The constitution of camphene has given rise to much discussion, but may now be regarded as settled in accordance with formula VI.

Camphene is a solid, melting at about 50°, with a smell of turpentine and camphor. When oxidised with chromic acid it yields camphor. If hydrogen chloride is passed into an ethereal solution of camphene there is formed *camphene hydrochloride* (VII), m.p. 125° to 127°. This very readily isomerises into *isobornyl chloride*[1] (VIII or IX), m.p. 161°. Recently it has been shown that camphene hydrochloride, isobornyl chloride and bornyl chloride exist in a state of equilibrium with one another, when in the fused state or in solution.[2] The *isomerism of bornyl and isobornyl chlorides and of the corresponding alcohols borneol and isoborneol* is most readily explained as arising from the *cis* or *trans* position of Cl or OH with respect to the $(CH_3)C<$ bridge across the cyclohexane ring (see formulæ VIIIa and IX in which the bracketed chlorine or

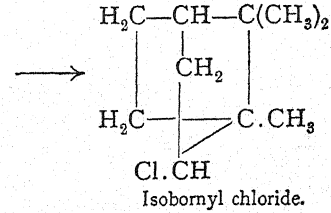
VI. Camphene



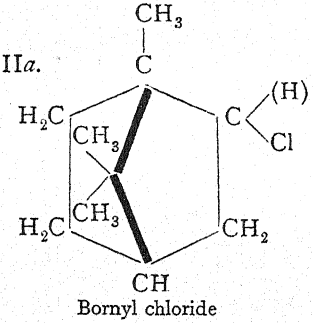
VII. Camphene hydrochloride



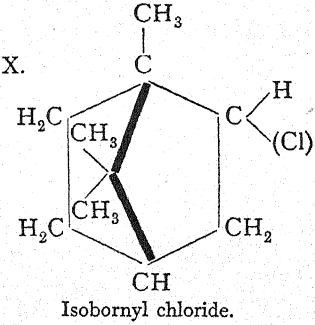
VIII. Isobornyl chloride.



VIII*a*. Bornyl chloride



IX. Isobornyl chloride.



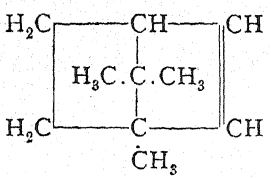
hydroxyl is supposed to lie behind the plane of that part of the ring structure to which it is attached). Although this problem has not been solved beyond dispute it appears probable that bornyl chloride and borneol are represented by *exo*-structures in which Cl or OH is in the *cis* position to the bridge, and that isobornyl chloride and isoborneol have the alternative *endo*-structures with a *trans* arrangement.[3] Corresponding to bornyl

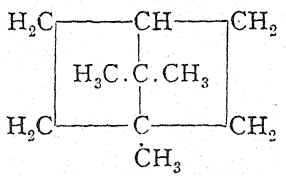
[1] Meerwein and van Emster, *Ber.*, 1920, **53**, 1821. [2] Meerwein and van Emster, *Ber.*, 1922, **55**, 2500. [3] G. Komppa and S. Beckmann, *Ann.*, 1936, **522**, 137. K. Alder and G. Stein, *Ann.*, 1934, **514**, 222. J. Bredt, *J. pr. Chem.*, 1929, (2), **121**, 153. Y. Asahina, *Ber.*, 1936, **69**, 343.

and isobornyl chlorides are the two stereoisomeric secondary alcohols *borneol* (formula V, p. 482) and *isoborneol*. Borneol can be obtained in considerable proportion from *both* of the above chlorides by way of the magnesium compounds, but camphene hydrochloride yields a larger proportion of isoborneol.[1]

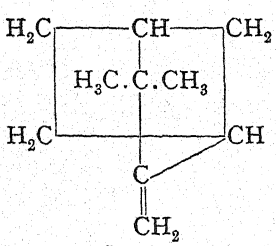
As may be seen from its formula, camphene is not related directly to camphane. An unsaturated derivative of camphane is *bornylene* (see below), which may be prepared by treating bornyl iodide with alkalis. The structures assigned to camphene and bornylene are confirmed by their reactions with diazo-acetic ester. With unsaturated compounds this ester normally yields nitrogen and a cyclopropane derivative, formed by union of the residue >CH.COOEt with the two C-atoms of the double bond. Camphene should thus give a structure , which on oxidation should yield a 1 : 1 : 2-tricarboxylic acid of cyclopropane. Similarly, bornylene should yield a 1 : 2 : 3-tricarboxylic acid. Both of these changes have been found to take place.[2]

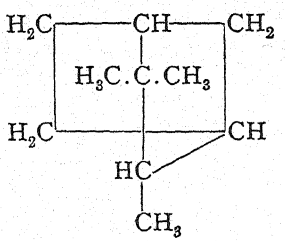
Camphane, $C_{10}H_{18}$, is dihydro-bornylene, since it is formed by the hydrogenation of bornylene :


Bornylene


Camphane (dihydro-bornylene)

whereas camphene corresponds to isocamphane.[3]


Camphene


Dihydro-camphene (isocamphane.)

Camphane is obtained from the bornyl chloride and isobornyl chloride already described. Both of these are readily converted into the magnesium compounds, which on decomposition with water yield camphane.[4] The latter melts at 153°, boils at 160°, and very readily sublimes. Camphane is also produced from borneol when the hydroxyl group is replaced by iodine, and the resulting bornyl iodide is reduced. It possesses a symmetrical structure and is thus optically inactive.

[1] A. Hesse, *Ber.*, 1906, **39**, 1136. For the conversion of borneol or isoborneol into camphene see Lipp, *Ber.*, 1920, **53**, 769. [2] Büchner and Weigand, *Ber.*, 1913, **46**, 258, 2013. [3] The nomenclature of this group, which is the result of its historical development, is confusing and requires modification. [4] A. Hesse, *Ber.*, 1906, **39**, 1128.

Alcohols and Ketones

Borneol, Borneo-camphor, *camphol*, $C_{10}H_{17}.OH$ (formula V, p. 482), melts at 203° and boils at 212°. It exists in nature in the *d*-, *l*- and *r*-forms. d-*Borneol* is found in a tree, *Dryobalanops camphora*, growing in Sumatra and Borneo, and also in rosemary and spike oils; *l*-borneol and the inactive variety occur in valerian oil. The formation of borneol from pinene and camphene hydrochlorides has already been described. It is related to ordinary camphor as a secondary alcohol to the corresponding ketone, and hence may be converted into camphor by oxidation with nitric acid or prepared from it by reduction with sodium and alcohol. Borneol resembles camphor in smell and burning taste. When warmed with potassium bisulphate it parts with water and yields camphene. It has already been mentioned that bornyl chloride is identical with "pinene hydrochloride." *Isoborneol*, m.p. 212°, is a stereoisomeride of borneol which does not occur naturally; it may be obtained in the form of its acetate by warming camphene with glacial acetic acid and concentrated sulphuric acid at 50° to 60°. If isoborneol dissolved in xylene is treated with sodium it is transformed into *borneol*. With oxidising agents such as permanganate, ozone, chlorine or oxides of nitrogen, it is readily converted into camphor. The relationship between borneol and isoborneol has already been dealt with on p. 483.

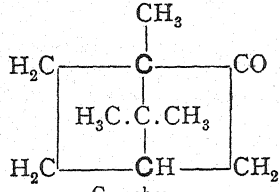
Camphor, Japanese camphor, $C_{10}H_{16}O$, was until recently obtained exclusively from the camphor tree, *Laurus camphora*, growing in Japan (particularly in Formosa) and China. For this purpose the wood is heated with water, when camphor and camphor oil pass over with the steam. The vapours are condensed in a suitable manner and the camphor is removed and purified by sublimation. It forms a colourless, transparent mass of characteristic smell and burning taste, m.p. 175° and b.p. 209°. In alcoholic solution it is dextrorotatory. The world's consumption of camphor is considerable, since it is used in the manufacture of celluloid, explosives and perfumes, and also in medicine. For this reason the industrial preparation of camphor from pinene (p. 488) is of great importance. With the exception of that used for therapeutic purposes, the demand for camphor in Germany is almost entirely met by the artificially prepared product.

l-*Camphor*, the optical antipode of *d*-camphor, occurs in the oil of *Matricaria parthenium*, and apart from the sign of its rotation, shows the same properties as ordinary camphor. By mixing the two antipodes, *r*-camphor, m.p. 178°, is obtained, identical with that produced by the oxidation of *r*-borneol or *r*-camphene.

Constitution of Camphor.—The first suggestion as to the constitution of camphor was advanced in 1859 by Berthelot, and for the next forty years numerous workers were engaged on the problem. Information has been gained chiefly by the degradation of the camphor molecule by oxidation, and a series of detailed investigations on these lines finally led

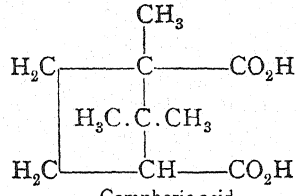
Bredt [1] to put forward a constitution (formula X) which is now generally accepted as correct.

X.



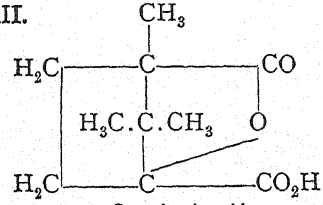
Camphor

XI.



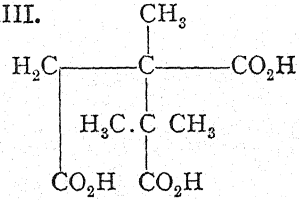
Camphoric acid

XII.



Camphanic acid

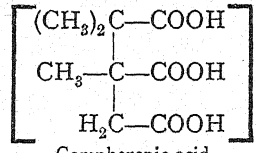
XIII.



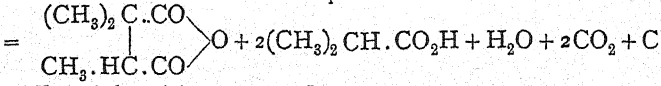
Camphoronic acid.

The oxidation of camphor with nitric acid leads to the formation of *camphoric acid*, $C_{10}H_{16}O_4$, *camphanic acid*, $C_{10}H_{14}O_4$, and *camphoronic acid*, $C_9H_{14}O_6$, as chief products. These three acids represent different stages of oxidation, and camphoronic acid itself may be obtained by the continued oxidation of either of the other two.

Two facts established by Bredt are of special significance in connection with the constitution of camphoronic acid. It is a tribasic acid which resembles tricarballylic acid in its properties. On slow oxidation it breaks up mainly to form carbon dioxide, isobutyric acid and trimethyl-succinic acid. From this behaviour Bredt concluded that camphoronic acid was trimethyl tricarballylic acid, a view confirmed later by its synthesis by Perkin and Thorpe.[2]



Camphoronic acid.



Trimethyl-succinic anhydride

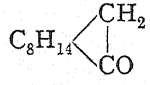
Isobutyric acid.

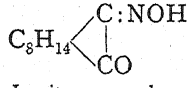
Since camphoronic acid is an oxidation product of camphanic acid, camphoric acid and camphor, it may be concluded that the carbon framework of camphoronic acid is present in each of these compounds, thus leading to the formulæ shown above. Trimethyl-succinic acid has also

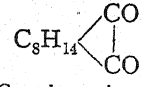
[1] Bredt, *Ber.*, 1893, **26**, 3047; **27**, 2092; **28**, 316. *Ann.*, 1896, **292**, 55; **299**, 131. See also Lapworth, *B. A. Rep.*, 1900, 299. [2] *J. C. S.*, 1897, **71**, 1169.

been prepared directly from camphoric acid by oxidation with chromic acid. The constitution of camphoric acid has in addition been confirmed synthetically (see below).

The ketonic character of camphor is proved by the formation of an oxime, C_9H_{16}:C:NOH (m.p. 118°, b.p. 249°), and the position of the CO-group is shown by the conversion of camphor into carvacrol, $C_{10}H_{14}O$ (see p. 424), on boiling with iodine. In the latter compound the hydroxyl is in the ortho-position to a methyl group. The presence of the group CH_2.CO in camphor follows from the production of *isonitroso-camphor* (m.p. 153°) on treatment with amyl nitrite and sodium alcoholate. When this substance is boiled with dilute sulphuric acid it yields *camphor-quinone* (m.p. 198°).


Camphor

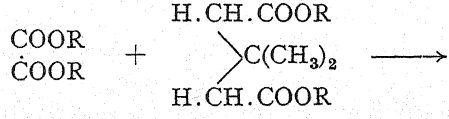

Isonitroso-camphor.


Camphor-quinone.

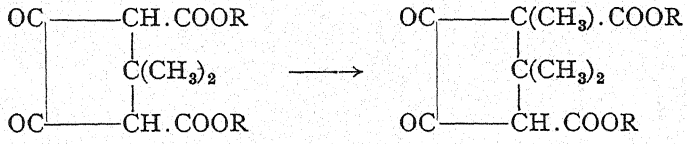
Among other reactions camphor yields *p*-cymene by loss of water when it is heated with P_2O_5.

Synthesis of Camphor.—The most convincing proof of Bredt's formula for camphor is provided by Komppa's synthesis [1] of camphoric acid, from which camphor itself had previously been obtained.[2] The method employed was as follows: The dimethyl ester of *ββ*-dimethyl-glutaric acid (XV) was condensed with oxalic ester (XIV) to give diketo-apocamphoric ester (XVI). From this, by treatment with metallic sodium and methylation with methyl iodide, was obtained diketo-camphoric ester (XVII), which by way of various intermediate compounds was reduced to r-*camphoric acid* (XVIII), m.p. 200° to 202°.

XIV. XV.



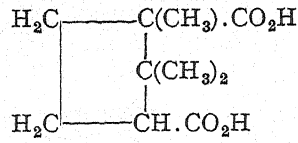
XVI. XVII.



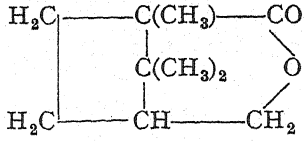
Camphoric anhydride, when treated with sodium amalgam, can also be converted into the lactone, campholide (XIX), which with potassium cyanide yields the nitrile of homocamphoric acid (XX). The calcium salt of this acid, on distillation, finally gives the corresponding ketone, camphor (XXII).

[1] Komppa, *Ann.*, 1909, **368**, 126; **370**, 209. [2] Bredt and Rosenberg, *Ann.*, 1896, **289**, 1.

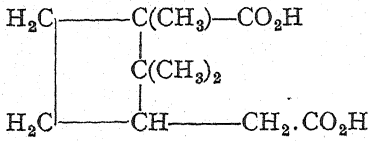
XVIII.



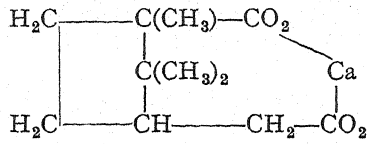
XIX.



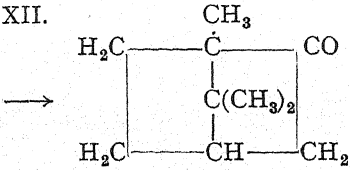
XX.



XXI.



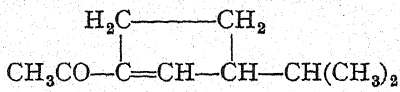
XXII.



Another synthesis of camphoric acid has been effected by Perkin and Thorpe.[1]

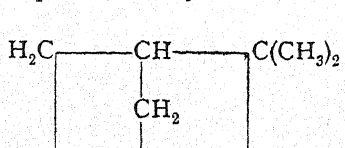
Camphor is now prepared industrially from pinene. The latter can be converted in a variety of ways into borneol or isoborneol (*e.g.* pinene ⟶ bornyl chloride ⟶ isobornyl acetate ⟶ isoborneol) and thence by oxidation into camphor. The name "artificial camphor" as applied to bornyl chloride is unfortunate.

Contrary to the earlier view, the compound known as *isocamphor* is now found to possess an entirely different structure to that of camphor.[2] It contains a five-membered ring and is a Δ^1-1-acetyl-isopropyl-cyclopentene of the formula

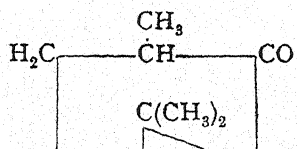


Other ketonic derivatives of the dicyclic terpenes are fenchone and carone.

Fenchone,[3] m.p. 5°, b.p. 192° to 194°, is very similar to camphor in its behaviour. It is found as the *d*-enantiomorph in fennel oil, and as the *l*-compound in thuja oil.



Fenchone



Carone.

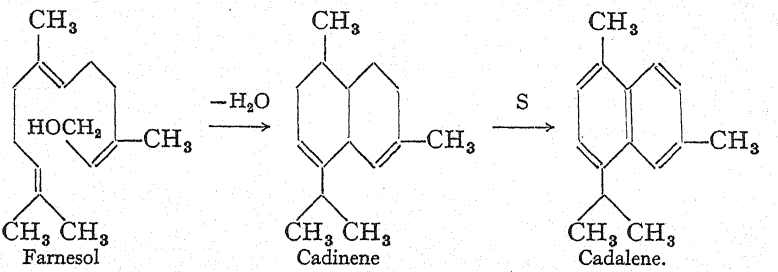
Carone (b.p. 100°/15 mm.) is a ketone derived from the hydrocarbon, carane. It does not occur naturally but can be prepared from carvone.

[1] *J. C. S.*, 1906, **89**, 795. [2] Wallach and Schlubach, *Ann.*, 1912, **392**, 69. [3] Wallach, *Ann.*, 1909, **369**, 63.

Sesquiterpenes and Diterpenes

Considerable progress has been made during the last few years in the investigation of higher terpenes, especially the sesquiterpenes.

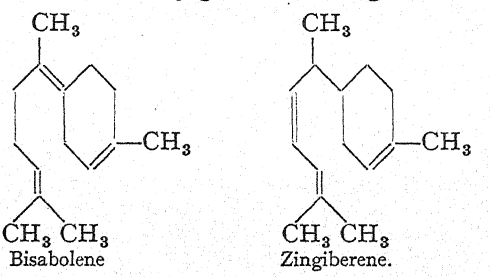
Sesquiterpenes include hydrocarbons of the formula $C_{15}H_{24}$ and their oxygen derivatives, and are found widely distributed in essential oils. Some of the members of this group are **open-chain compounds** (*farnesol*), others are **monocyclic** (*bisabolene, zingiberene*) and still others **dicyclic** (*cadinene, eudesmol*). Much of our knowledge of these compounds is due to Ruzicka,[1] Simonsen and others. The relationships among the sesquiterpenes may be illustrated by the conversion of the open-chain alcohol *farnesol* by loss of water into the dicyclic hydrocarbon



Farnesol Cadinene Cadalene.

cadinene. By fusion with sulphur (Veresterberg's dehydrogenation method) the latter has been converted into cadalene, 1 : 6-dimethyl-4-isopropyl-naphthalene, thus giving valuable information as to its structure.

Among *monocyclic sesquiterpenes* may be mentioned *bisabolene* (from oil of lemons) and its isomeride *zingiberene* (in oil of ginger). The former may be obtained from farnesol by gentle warming with strong acids.



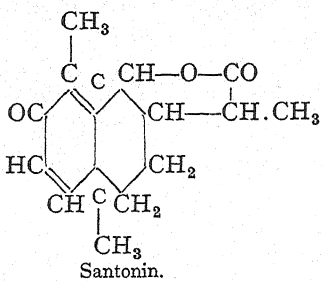
Bisabolene Zingiberene.

The *dicyclic sesquiterpenes* are related to naphthalene in much the same manner as the terpenes are to benzene, some (e.g. *cadinene*, in oil of cubebs) being derived from cadalene, others (e.g. *eudesmol*, in eucalyptus oil) from eudalene, 1-methyl-7-isopropyl naphthalene, and similar types.

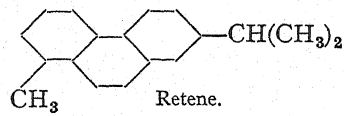
Santonin, $C_{15}H_{18}O_3$, m.p. 170°, $[\alpha]_D = -171°$, is the active constituent of wormseed (*Artemisia Santonica*). Clemo and Haworth[2] have shown that it possesses the annexed formula, a modification of an earlier

[1] See L. Ruzicka, *Über Konstitution und Zusammenhänge in der Sesquiterpenreihe* (Berlin, 1928). [2] G. R. Clemo, R. D. Haworth and E. Walton, *J. C. S.*, **1929**, 989; **1930**, 1110. Clemo and Haworth, *J. C. S.*, **1930**, 2579. The above constitution is also adopted by Ruzicka, *Helv. Chim. Acta*, 1930, **13**, 1117.

suggestion of Cannizzaro. It is thus a lactone closely related to the eudesmol group of terpenes.



Santonin.



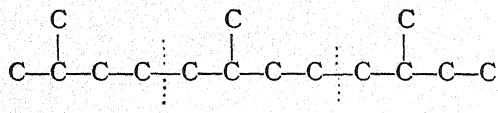
Retene.

Comparatively little is known about the **diterpenes**, $C_{20}H_{32}$, which occur chiefly in vegetable resins and balsams. The best known representative is the carboxylic compound, *abietic acid*, ($C_{20}H_{30}O_2$), which forms the chief constituent of ordinary rosin (colophonium). On being heated with sulphur abietic acid yields retene, 1-methyl-7-isopropyl-phenanthrene.

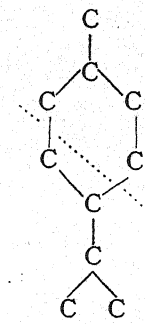
Squalene,[1] $C_{30}H_{50}$, is an open-chain **dihydro-triterpene** obtained from the livers of certain fish.

Isoprene and Terpene Structure

With very few exceptions all terpenes of known constitution, whether simple or complex, open-chain or cyclic, have been found to possess a molecular structure built up of a complete number of isoprene units.



Open-chain sesquiterpene.

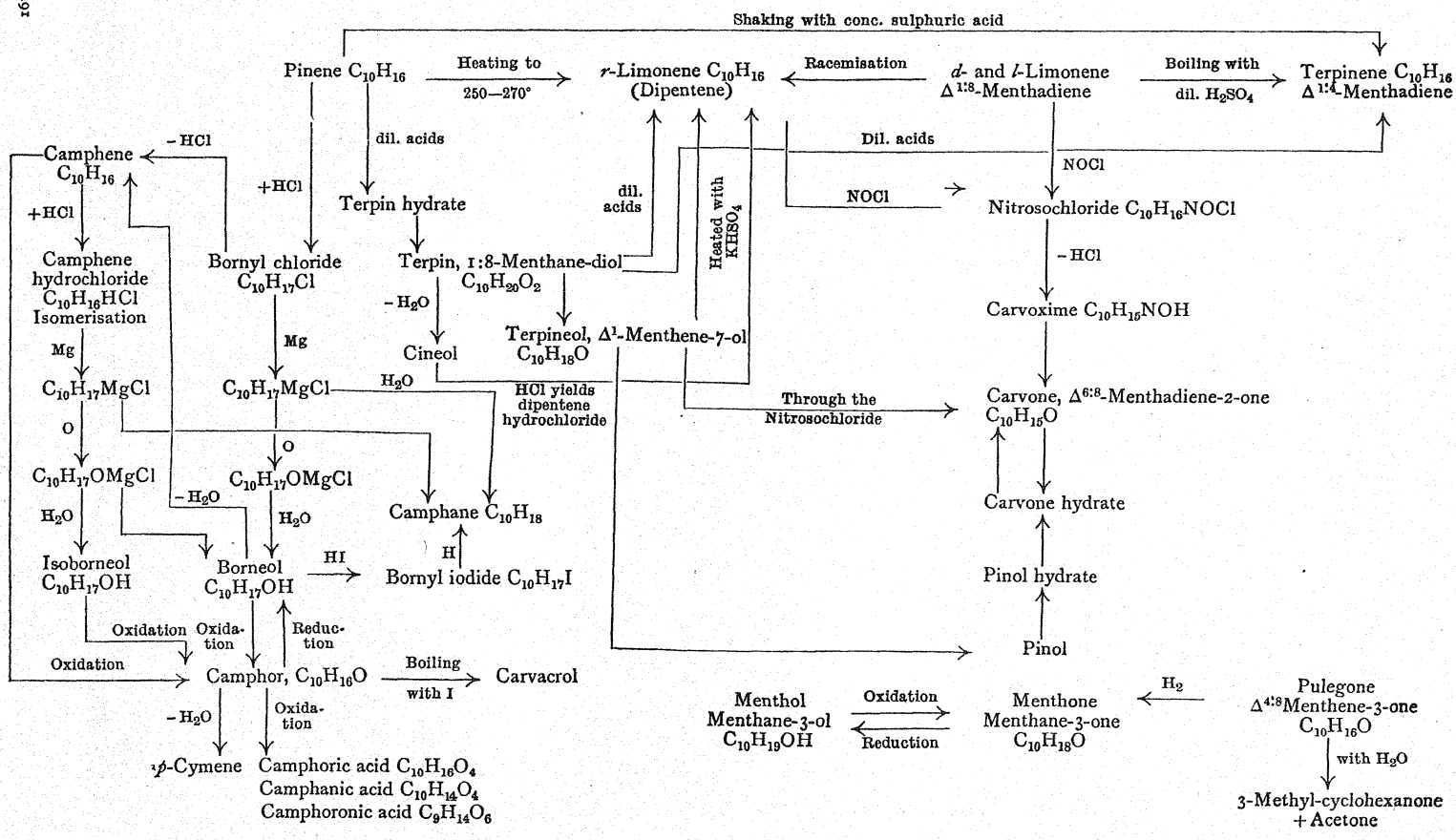


Monocyclic terpene.

This relationship possibly indicates a common origin in the form of some reactive 5-carbon compound such as isovaleraldehyde, $(CH_3)_2CH.CH_2.CHO$, or of simpler products which may give rise to it, a speculation which is supported by the occurrence of isovaleraldehyde (and of acetone and acetaldehyde) in a number of essential oils. It has been suggested that these substances by condensation and reduction may give rise to citral or geraniol and thus to various more complex derivatives.[2]

[1] Heilbron and co-workers, *J. C. S.*, **1926**, 1630, 3131; **1929**, 873, 883. [2] Compare Kremers, *J. Biol. Chem.*, 1922, **50**, 31. J. Read, "Some Biogenetic Relationships in the Menthone Series," *J. S. C. I.*, 1929, **48** (*Chem. and Ind.*), p. 786.

Transformations and Degradations in the Terpene and Camphor Series.



RUBBER [1]

Rubber is obtained from the sap of a number of trees belonging to the *Apocynaceæ*, *Moraceæ* and *Euphorbiaceæ* families. These are found in tropical countries, particularly in South America, Africa and the East Indies. The most valuable rubber tree is the *Hevea brasiliensis*. The bark of the tree is " tapped " by making a small incision and the milky *latex* which oozes out is collected in pans. The latex is next polymerised, *e.g.* by subjecting it to the action of smoke, to give crude rubber. This is freed from admixed sand, bark and other impurities by boiling with water, when the mass becomes plastic. It is then kneaded between warm rollers until homogeneous, and finally rolled out into sheets. The product so obtained consists essentially of **caoutchouc,** the hydrocarbon constituent of rubber. It has no definite melting point, is insoluble in water, dilute acids and alkalis, but dissolves in benzene, carbon disulphide and chloroform. On dry distillation it yields isoprene (p. 125). With N_2O_3 the various forms of caoutchouc are generally converted into a nitrosite of the composition $(C_{10}H_{15}N_3O_7)_2$, a reaction which may be used technically for the quantitative estimation [2] of rubber in rubber goods.

Distillation of Caoutchouc.[3]—When subjected to dry distillation rubber decomposes to give a mixture of products, the more volatile of which boil as low as 25°, whilst others range above 300°. Of these products only two fractions have been carefully investigated, namely those boiling at 30° to 40° and 160° to 170° respectively. In the latter fraction is found *dipentene* (Wallach), and in the former *isoprene*, *dimethyl-allene* and *dihydro-isoprene*. This problem has been very largely cleared up by the work of Ipatieff, who also showed that isoprene could only be prepared in the pure state by indirect methods. The constitution of isoprene has been established by the syntheses of Euler and Ipatieff. Harries found that from 1500 gms. of good caoutchouc only 35 gms. of isoprene boiling at 33° to 34° could be obtained.

Synthesis of Rubber.—The first real synthesis of rubber is due to Tilden in 1892, who discovered that a sample of isoprene, prepared by heating dipentene, had in the course of some months polymerised into rubber. The technical application of this polymerisation was discovered independently in 1910 by Matthews [4] and Harries,[5] who showed that isoprene on being warmed for about 50 hours to 60° with sodium wire in a sealed tube, is practically quantitatively converted into a solid rubber. Harries showed that the polymerisation could also be effected, though less satisfactorily, by heating isoprene with glacial acetic acid to a temperature above 100° in a sealed tube. In this connection it has to be

[1] See *Chemistry of Rubber*, by B. D. N. Luff (Benn, 1923). C. D. Harries, *Untersuchungen über die naturlichen und künstlichen Kautschukarten* (Berlin, 1919). [2] Harries, *Ber.*, 1901, **34**, 2991; 1902, **35**, 3256, 4429; 1903, **36**, 1937; 1905, **38**, 87. [3] R. Willstätter, *Ber.*, 1911, **44**, 3423. [4] See Perkin, *J. S. C. I.*, 1912, **31**, 616. Strange and Graham, Eng. Pat. 24790, 1910. [5] Harries, *Ann.*, 1911, **383**, 184.

borne in mind that synthetic rubber is not identical with the natural product.

Constitution of Caoutchouc.—The molecular constitution of caoutchouc has not yet been solved, largely owing to the difficulties presented by its high molecular weight and peculiar physical properties, which render purification a difficult problem. Any suggested structure must conform to the following experimental facts.

1. Caoutchouc has the empirical formula $(C_5H_8)_n$, although the most highly purified samples so far prepared still have traces of N, O and S.

2. It is optically inactive and therefore probably contains no asymmetric carbon atom.

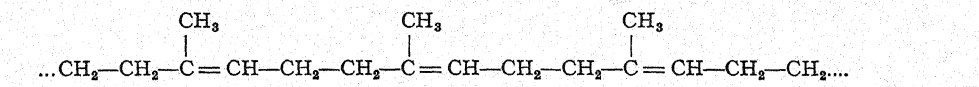
3. It appears to be a complex polymeride of isoprene, and yields a so-called *tetrabromide*, $(C_{10}H_{16}Br_4)_n$, and an *ozonide*, $(C_{10}H_{16}O_6)_n$. Hence the molecule has two double bonds for every ten carbon atoms (Harries).

4. The ozonide when boiled with water yields lævulinic aldehyde and its peroxide, together with laevulinic acid as a secondary oxidation product (Harries).

5. Hydrogenation experiments show that two hydrogen atoms are taken up for every eight already present.

Pummerer [1] in 1929 determined the molecular weight of highly purified caoutchouc in menthol and in camphor solution, using the cryoscopic method. The results indicated $(C_5H_8)_n$, where $n=16$ to 24, thus giving a molar weight of 1100 to 1600. Measurements of viscosity carried out by Staudinger, on the other hand, led him to assign n as high a value as 1300.

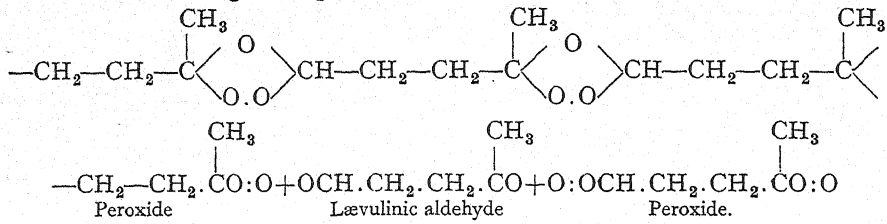
Any formula for caoutchouc must retain isoprene as the unit of structure in order to account for the production of lævulinic aldehyde on ozonisation, and of isoprene among other products on distillation. Further, the molecule would appear to be cyclic in view of the low percentage of hydrogen and degree of unsaturation. Pickles [2] has proposed a closed chain structure built up of an indeterminate number of C_5H_8 molecules.



Polymerisation is here represented as being purely chemical in nature, the union of isoprene molecules being accompanied by a rearrangement of the double bonds. The ozonide is assumed to be formed as a result of the separation of the carbon atoms at the points originally occupied

[1] *Ber.*, 1929, **62**, 2628. [2] *J. C. S.*, 1910, **97**, 1085.

by the double bonds, with the production of a compound having as its basis the following arrangement :



Water brings about decomposition of the ozonide at the points shown, with the formation of lævulinic aldehyde, lævulinic aldehyde peroxide, and some lævulinic acid as a further oxidation product of the aldehyde. An arrangement of the above type is also advocated by Staudinger,[1] who prefers, however, an open-chain formula.

It will thus be seen that the evidence bearing on the constitution of rubber is not conclusive. The possibility that it contains a mixture of polyterpene isomerides is supported by its indefinite physical characteristics as well as by the fact that isoprene, for example, may be polymerised by various agencies such as ultra-violet light, hydrogen chloride, acetic acid and sodium, to form products whose properties depend to some extent upon the agent employed.

Guttapercha strongly resembles rubber and is prepared from the sap of certain plants (Sapotaceae) found in Malacca and the East Indies. It is purified in a similar manner to rubber, and is extensively used for making moulds, as insulating material, etc. Guttapercha is also derived structurally from isoprene, and Staudinger has suggested that this compound and caoutchouc are represented by similar formulæ, differing chiefly in the arrangement of the groups around the double bonds, the former having a *cis* and the latter a *trans* configuration (*see also* p. 498).

Vulcanisation of Rubber.—Caoutchouc is remarkable for its great elasticity, but with rise of temperature it gradually loses this valuable property, and on being cooled it becomes hard. To minimise these defects the great bulk of the rubber used industrially is vulcanised, a process which also renders it stronger, more elastic and practically insoluble in the usual solvents. **Hot vulcanisation**, discovered in 1839 by Goodyear, is effected by mixing the dry material with sulphur and other ingredients, such as fillers, accelerators and anti-oxidants, and heating at 120-160°. Soft rubber goods made in this way contain from 3-10 per cent. of sulphur, hard rubber goods from 10 to 35 per cent. If the proportion of sulphur rises to 25-35 per cent., **ebonite** or **vulcanite** is formed, a hard product used as insulating material. Selenium has also been utilised for vulcanisation, generally in admixture with sulphur.

For special purposes **cold vulcanisation** is employed, involving immersion in sulphur monochloride, S_2Cl_2, dissolved in carbon disulphide or other suitable solvent. This method was introduced by Parkes in 1846, and is used for thin goods such as surgeon's gloves. Sulphur chloride

[1] *Ber.*, 1924, **57**, 1203 ; *Ann.*, 1929, **468**, 1.

may also be applied in the form of vapour. A recent special process for thin rubber, due to Peachey, is to submit it to the action of gaseous sulphur dioxide, followed after a period by hydrogen sulphide. Finely divided and highly reactive sulphur is thus deposited in the material, causing vulcanisation to proceed at ordinary temperatures. This method is not much used.

As will be seen later, raw rubber has a macromolecular structure of long open or possibly closed chains, built up from isoprene units and containing one double bond for every five carbon atoms. Such chains are comparatively readily separated from one another by solvents. In soft vulcanised rubber the greater part of the sulphur is merely adsorbed, but the remaining atoms have entered into combination at some of the points originally occupied by the double bonds [1] so as to form cross links which unite the chains laterally. The presence of thioether links can be proved by their additive reaction towards methyl iodide, which can be used as a means of estimating the proportion of sulphur bridges in a given sample.[2] It is this change in the molecular pattern which modifies the physical properties, giving greater rigidity and resistance to solvents. In ebonite the process has been carried so far that the bulk of the sulphur is in the combined state. The resulting hard product has an empirical formula approximating to C_5H_8S, and thus contains one atom of sulphur for each double bond present in the original raw rubber.

Accelerators.—In the absence of accelerators vulcanisation proceeds slowly. Until 1906 the only compounds added to speed up the reaction were metallic oxides, principally litharge, white lead, lime or magnesia. In that year Onslager discovered that organic amines were also effective and these are now used, often mixed with inorganic oxides. Among compounds of this type may be mentioned antimony sulphide, Sb_2S_5, hexamethylene tetramine, thiocarbanilide and a variety of dithiocarbamates and xanthogenates. In addition to reducing the time or lowering the temperature required for vulcanisation, the use of accelerators frequently improves the quality of the product, giving increased strength and greater resistance to abrasion.

Fillers are blended in a finely divided state with the " mix " in order to modify the stiffness, strength or other properties of the finished product. They may stiffen the vulcanised rubber without increasing the total energy necessary to extend a strip to the breaking point. Whiting, barytes and ground slate are used in this manner. On the other hand, " reinforcing " pigments may be added which lead to an increased energy being required to extend a strip to the breaking point. Carbon black is thus used in large proportions in the manufacture of motor tyres. Zinc oxide and magnesium carbonate are added for the same purpose.

Anti-oxidants are introduced into the mix in small quantities (0·5 to 2 per cent.) in order to delay oxidation and ageing of the rubber in light

[1] See, for example, K. H. Meyer and W. Hohenemser, *Helv.*, 1935, **18**, 1061. [2] Meyer and Mark, *Ber.*, 1928, **61**, 1928.

and air, which result in hardening, flex-cracking and loss of tensile strength. This is a later development of rubber technology, but already a very large number of compounds have been suggested and used for the purpose. Thus amines and amino-phenols, aldehyde amines, amino-ketones and their condensation products and various absorbents of ultra-violet light have been utilised. Raw rubber contains a considerable amount of a natural anti-oxidant which protects it from rapid deterioration, but the quantity present is insufficient for the protection of the rubber in the vulcanised state.

Synthetic Rubbers[1]

Polymerisation methods enable us to convert many hydrocarbons containing conjugated double bonds into rubber-like products, which may be vulcanised and worked up in the usual way. Industrial processes for preparing isoprene and analogous compounds are therefore of very great interest. Some of these are summarised below. It may be noted that the first two are now of historical interest only, and that large-scale production generally involves the dehydration of a butylene glycol by catalytic methods.[2]

(*a*) **Isoprene** can be obtained from fusel oil (isoamyl alcohol) by treatment with hydrochloric acid to form isoamyl chloride, followed by chlorination to a dichloro-pentane. On being passed over soda lime at 470°, this last loses hydrogen chloride and yields isoprene.

$$(CH_3)_2CH.CH_2.CH_2OH \longrightarrow (CH_3)_2CH.CH_2.CH_2Cl \longrightarrow (CH_3)_2CCl.CH_2.CH_2Cl \longrightarrow CH_2:C(CH_3).CH:CH_2$$

(*b*) **Dimethyl-butadiene** is prepared from starch as the raw material. In the Fernbach process starch is converted into acetone by fermentation using a special anærobic micro-organism. The acetone is then reduced with aluminium foil to pinacol, which in contact with alumina at 400° loses water to form dimethyl-butadiene.

$$\text{Pinacol}\quad \begin{matrix} CH_3.C(OH).CH_3 \\ | \\ CH_3.C(OH).CH_3 \end{matrix} \longrightarrow \begin{matrix} CH_3.C:CH_2 \\ | \\ CH_3.C:CH_2 \end{matrix} \quad \text{Dimethyl-butadiene}$$

(*c*) In Russia alcohol prepared from grain or potatoes is converted into **butadiene** by a catalytic process due to Lebedev (1933). The superheated vapour of crude alcohol is passed through an electrically heated chamber packed with oxides of aluminium and zinc.

$$2C_2H_5.OH \longrightarrow CH_2:CH.CH:CH_2+2H_2O.$$

Unchanged alcohol is removed in a condenser at 0° and the butadiene "scrubbed" out of the emerging gases with the aid of turpentine. Butadiene is recovered by distillation and polymerised to rubber by use of sodium.

Alternatively, alcohol is converted into butadiene by the method of Ostromisslensky, namely (1) $C_2H_5OH \longrightarrow CH_3.CHO$, followed

[1] See *Synthetic Rubber*, by W. J. S. Naunton (Macmillan, 1937). [2] These have been developed out of the patented process of Matthews, Strange and Bliss (E.P. 3873, 1912).

by (2) $C_2H_5.OH + CH_3.CHO \longrightarrow CH_3.CHOH.CH_2.CH_2OH \longrightarrow CH_2:CH.CH:CH_2$.

(*d*) **Buna rubber** is manufactured in considerable quantities in Germany from acetylene. The various steps are believed to be as follows. Acetylene is converted into acetaldehyde by catalysis in the presence of sulphuric acid and mercuric sulphate and the aldehyde then condensed to aldol. The latter is reduced electrolytically to 1:3-butylene-glycol and this dehydrated catalytically to butadiene.

$$CH:CH \longrightarrow CH_3.CHO \longrightarrow CH_3.CHOH.CH_2.CHO \longrightarrow CH_3.CHOH.CH_2.CH_2OH \longrightarrow CH_2:CH.CH:CH_2$$

In the final stages of manufacture the polymerised product is vulcanised in the same way as natural rubber.

The Buna rubbers are of two main types, distinguished by use of numbers or letters. Thus **Buna 1, Buna 2,** etc., are believed to be direct polymerisation products of butadiene, the numbers having some relation to the average molecular chain lengths as indicated by the viscosities of the corresponding solutions. These are soft rubbers, which however make excellent ebonites on vulcanisation.

Another type is produced by interpolymerisation of butadiene with other polymerisable compounds such as styrene (**Buna S**) and acrylic nitrile (**Buna N**). In these products the long macro-molecules of polymerised butadiene are assumed to be cross-connected by shorter links built up from styrene or acrylic nitrile, resulting in a considerable modification of the structural pattern. The interpolymers are more rigid, respond less to heat treatment, are resistant to solvents and are more difficult to work up. A property of technical importance is their greater resistance to abrasion and oxidation.

Polymerisation is effected by use of sodium (about 0·5 per cent.) deposited on an iron wire comb, at a temperature not above 65° and over a period of about 90-120 hours. This is followed by a " ripening " period of 3-8 days at 40°. The yield under optimum conditions rises to 83 per cent.

Emulsion polymerisation is more convenient for the production of interpolymers such as Buna S and Buna N. Thus a mixture of butadiene with 10 to 30 per cent. of acrylic nitrile is emulsified with a 5 per cent. aqueous solution of the hydrochloride of diethylamino-ethyloleylamide, containing a small amount of trichloracetic acid. Polymerisation is quantitative in 3-4 days at 50-60°.

Synthetic rubbers of the types referred to under (*c*) and (*d*) are manufactured to replace natural rubber. They are more expensive than the latter, but can be made from raw materials such as grain or coal, which do not require to be imported. As has been indicated above, the properties of the final product can be varied by interpolymerisation in a manner not possible with plantation rubber.

(*e*) **Neoprene, duprene** is a rubber-like material containing chlorine, which has been developed in America. Acetylene is first submitted to

controlled polymerisation in the presence of aqueous cuprous chloride to give vinyl-acetylene. From this by reaction with hydrogen chloride is obtained *chloroprene* (chlorobutadiene) which automatically polymerises to neoprene on standing.

$$2C_2H_2 \longrightarrow \underset{\text{Vinyl acetylene}}{CH_2:CH.C:CH} \longrightarrow \underset{\text{Chloroprene.}}{CH_2:CH.CCl:CH_2} \longrightarrow \text{Neoprene}$$

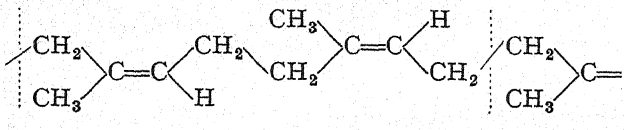
On oxidation with nitric acid neoprene yields succinic acid.[1] This is in agreement with the structure given below, and with its X-ray diagram.

$$-CH_2.\underset{\underset{Cl}{|}}{C}=CH.CH_2.CH_2.\underset{\underset{Cl}{|}}{C}=CH.CH_2- \longrightarrow HOOC.CH_2.CH_2.COOH$$

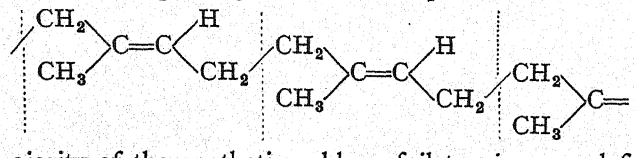
Neoprene is an elastic product which before it is worked up resembles smoked sheet rubber in appearance. It does not require vulcanisation, but is compounded with other suitable ingredients such as magnesia, wood rosin and zinc oxide prior to being made into manufactured articles. Neoprene is superior to natural rubber in its resistance to oils, heat, light and ozone, and is less permeable to gases. Although more costly than rubber it is therefore used for making transmission belts, printing rollers and flexible tubing employed for the conveyance of oil and petrol.

X-ray Analysis of Natural and Synthetic Rubbers

In 1925 it was observed by Katz [2] that when a piece of clear unvulcanised natural rubber is strongly stretched it becomes opalescent and then gives an interference fibre diagram if examined by means of X-rays. Subsequent work by K. H. Meyer,[3] who used stretched films of thin rubber, showed that the distance between repeating units in the fibre axis corresponded to two isoprene residues, from which it may be deduced that the CH_2 groups occupy *cis* positions about the double bonds.



Similarly, it is concluded that guttapercha [3] is the corresponding *trans*-isomer, with a repeating unit of one isoprene residue.



The majority of the synthetic rubbers fail to give any definite X-ray diagrams on being stretched, probably because of irregularities arising

[1] W. H. Carothers, I. Williams, A. M. Collins and J. E. Kirby, *J. A. C. S.*, 1931, 53, 4208.
[2] *Naturwiss.*, 1925, 13, 410. [3] K. H. Meyer and H. Mark, *Ber.*, 1928, 61, 1939.

from cross-linking of the fibres. An exception is found in neoprene, for which Kenney [1] finds an identity period along the fibre axis corresponding closely to one isoprene unit. Neoprene therefore probably possesses a *trans* configuration, similar to that of guttapercha but with chlorine atoms replacing the methyl groups.

XIII

Compounds containing Benzene Nuclei united by Carbon Linkings

Many of the methods described in the foregoing sections for introducing alkyl groups into the benzene nucleus may also be employed for the introduction of phenyl, benzyl and other aromatic groups. In this way compounds are formed containing benzene nuclei linked together directly, or through the medium of one or more carbon atoms. The simplest examples of this kind are in the diphenyl group.

I.—DIPHENYL GROUP

Diphenyl, *phenyl benzene,* $C_6H_5.C_6H_5$, the parent hydrocarbon of this series, is formed when benzene vapour is passed through a red-hot tube. It is best prepared by *Ullmann's* method, in which iodobenzene is heated to 220° with finely-divided copper.

$$2C_6H_5I+2Cu = C_6H_5.C_6H_5+Cu_2I_2$$

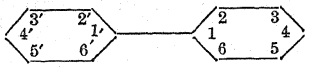
This process recalls Fittig's synthesis, but is of far greater general utility. It can be applied successfully to a variety of iodo and bromo substitution products of benzene, with the production of symmetrical diphenyl derivatives.[2] In the majority of cases the reaction between copper and the iodo-compound proceeds at 210° to 220°, and the constitution of the synthetic product can be deduced directly from that of its components. Bromo compounds, especially those in which the halogen atom is activated by an electronegative group in the ortho or para position, also react readily.

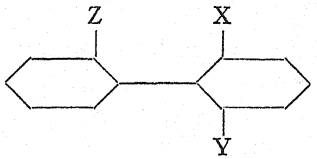
Diphenyl is also found in coal tar. It forms colourless crystals which melt at 70°, boil at 254°, and are readily soluble in alcohol and ether. With ozone it yields a *tetra-ozonide.*

The position of substituents in the diphenyl molecule is usually indicated by numbers as in formula I. With two or more substituents it will be seen that there are numerous possibilities of isomerism. In addition, isomerism of a new type may occur when three or four of

[1] A. W.Kenney, *J. A. C. S.*, 1931, 53, 4207. [2] Compare Ullmann, *Ann.*, 1905, 332, 38.

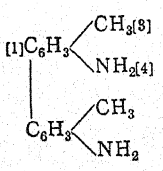
the ortho-positions to the common bond joining the benzene nuclei are substituted as in II (X and Z may also be identical). This isomerism is discussed fully on p. 43.

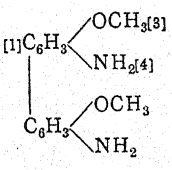
I. 

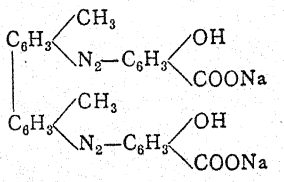
II. 

Benzidine, 4 : 4′-*diamino-diphenyl,* $NH_2.C_6H_4.C_6H_4.NH_2$, is obtained as described on p. 401 by intramolecular rearrangement of hydrazo-benzene. In its technical preparation nitrobenzene is reduced with zinc dust and sodium hydroxide, and the hydrazo-benzene so formed is converted into benzidine by heating with acid. The compound may either be isolated as the free base by addition of sodium hydroxide, or as the sparingly soluble sulphate. Benzidine crystallises from hot water in leaflets, m.p. 122°, and is largely used in the manufacture of substantive azo-dyes (see p. 412 *et seq.*). The *sulphonic acids* obtained by the action of concentrated sulphuric acid on benzidine are employed for the same purpose.

Tolidine (I), m.p. 128°, is a homologue of benzidine and is prepared in a similar manner from *o*-nitrotoluene; ***o*-dianisidine** (II) is obtained from *o*-nitroanisole, $C_6H_4(NO_2)OCH_3$.

I. 

II. 

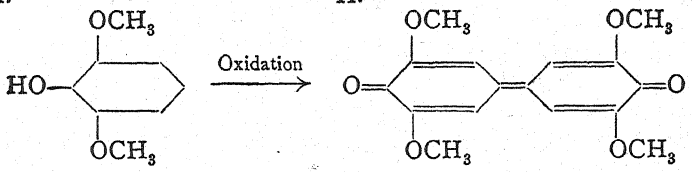
III. 

The first of these, on diazotisation and coupling with α- or β-naphthylamine sulphonic acids, yields the **benzo-purpurines** (B, 4B, 6B). These are red substantive dyes, and are less sensitive to acids than Congo red. From diazotised benzidine or tolidine and salicylic acid are obtained yellow substantive dyes known as **chrysamines** (*e.g.* compound III). *Diamine black* is prepared by coupling diazotised benzidine or dianisidine with aminonaphthol-sulphonic acid-G (2 : 8 : 6) in alkaline solution.

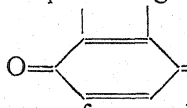
Hexahydroxy-diphenyl, $(HO)_3C_6H_2.C_6H_2(OH)_3$, crystallises from hot water in colourless needles, which darken above 200° and then gradually melt with decomposition. It is formed when pyrogallol dissolved in aqueous baryta is oxidised in air. A second hexahydroxy-diphenyl can be obtained from coerulignon. **Coerulignon** or *cedriret,* $C_{16}H_{16}O$, is a bluish-violet powder obtained during the purification of crude wood vinegar with potassium bichromate. It is regarded as a **tetramethoxy-diphenoquinone** (II), a view confirmed by its synthesis by A. W. Hofmann, by oxidation of the pyrogallol dimethyl ether occurring in beech tar.

Since this ether had been proved [1] to possess the structure I, coerulignon must be written as II.

I. II.

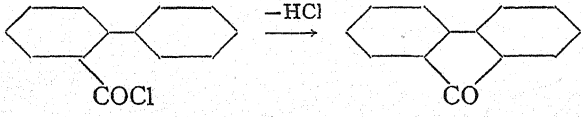


On reduction coerulignon yields **hydro-coerulignon,** which is represented as a tetramethyl ether of hexahydroxy-diphenyl. It melts at 190°, and on being heated with concentrated hydrochloric acid is converted into a hexahydroxy-diphenyl, differing from that obtained by oxidation of pyrogallol.

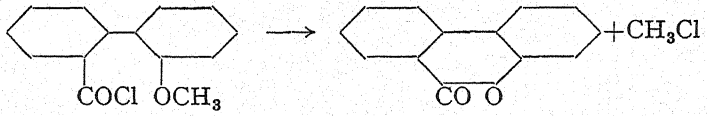
Other *diphenoquinones* or coerulignons have been prepared by Auwers,[2] who has shown the close relationship existing between these compounds and the *methylene-quinones*,  , which play an important rôle as the parent substances of many dye-stuffs, and as intermediate products in the transformations of pseudophenols. These two classes resemble one another in chemical behaviour, particularly in their strong additive properties.

Diphenyl-2-carboxylic acid, m.p. 111°, is obtained by fusing *fluorenone* (p. 505) with potassium hydroxide.

On treatment with strong sulphuric acid fluorenone is regenerated by removal of the elements of water. A similar ring closure is undergone by the acid chloride on distillation.[3]



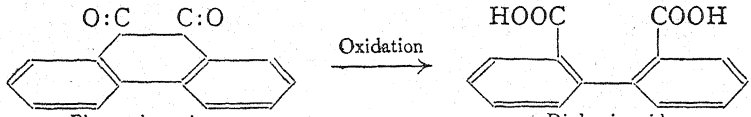
The acid chloride of 2′-*methoxy-diphenyl-2-carboxylic acid* loses methyl chloride spontaneously at ordinary temperatures to form the lactone of the 2′-hydroxy acid.[4]



These changes are promoted by the proximity of the reacting atoms or groups in the 2 : 2′-positions (see also isomerism of diphenyl derivatives, p. 43).

[1] Herzig and Pollak, *Monat. f. Chem.*, 1904, **25**, 501. [2] Auwers and Markovits, *Ber.*, 1905, **38**, 226. [3] C. Graebe and Rateanu, *Ann.*, 1894, **279**, 261. [4] H. G. Rule and E. Bretscher, *J. C. S.*, 1927, 925.

Diphenic acid, *diphenyl-2:2'-dicarboxylic acid*, m.p. 229°, is obtained by oxidising phenanthraquinone with a mixture of potassium bichromate and sulphuric acid. This reaction has given valuable information as to the constitution of phenanthrene.

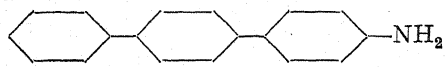


Phenanthraquinone Diphenic acid.

In the same manner substituted diphenic acids may be prepared from substituted phenanthraquinones.[1]

Another method of preparing diphenic acid is by the action of an ammoniacal solution of cuprous oxide on diazotised anthranilic acid.[2] When heated with soda lime it yields diphenyl, and on strong oxidation is converted into phthalic acid.

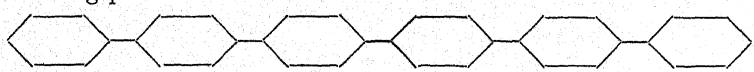
A number of hydrocarbons built up of a series of benzene rings linked together in the *p*-positions have recently been prepared. **Terphenyl,** p-*diphenyl-benzene*, m.p. 210°, was obtained by the interaction of azobenzene, benzene, hydrogen chloride and aluminium chloride. An intermediate product in the process is *amino-terphenyl*, which was deaminated in the usual way (p. 404).



The corresponding nitro-terphenyl has also been prepared by the interaction of *p*-nitrophenyl diazo hydroxide with diphenyl.[3] By converting

$$NO_2.C_6H_4.N_2OH+C_6H_5.C_6H_5 = NO_2.C_6H_4.C_6H_4.C_6H_5+N_2+H_2O$$

amino-terphenyl into the iodo-compound and heating the latter with silver powder at 330° (*Ullmann's* method) **sexiphenyl,** m.p. 475°, has been prepared.[4] These are colourless hydrocarbons which sublime well below their melting-points.



II.—DIPHENYL-METHANE AND FLUORENE GROUPS

Diphenyl-methane, *benzyl-benzene*, $C_6H_5.CH_2.C_6H_5$, forms needles, m.p. 26° and b.p. 262°, and has an odour of oranges. It may be obtained by the following methods :—

1. By the action of benzyl chloride, or of methylene chloride, on benzene in the presence of aluminium chloride.

$$C_6H_5.CH_2Cl+H.C_6H_5 \xrightarrow{-HCl} C_6H_5.CH_2.C_6H_5 \xleftarrow{-2HCl} 2C_6H_5.H+CH_2Cl_2$$

Various substitution products of benzene may also be employed (*e.g.*

[1] J. Schmidt and co-workers, *Ber.*, 1903, **36**, 3729; **37**, 3551. [2] Vorländer and Meyer, *Ann.*, 1902, **320**, 122. [3] H. France, I. M. Heilbron and D. H. Hey, *J. C. S.*, 1938, 1364. [4] Pummerer and Bittner, *Ber.*, 1924, **57**, 84.

homologues, phenols, tertiary amines), leading to the formation of ring-substituted diphenyl-methanes.

2. By the condensation of benzyl alcohol with benzene under the influence of concentrated sulphuric acid.

$$C_6H_5.CH_2OH+HC_6H_5 = C_6H_5.CH_2.C_6H_5+H_2O$$

Homologues of diphenyl-methane containing substituents in the methylene group are obtained in a similar manner by condensing aliphatic aldehydes or ketones with benzene, *e.g.*,

$$CH_3.CHO+2HC_6H_5 = CH_3.CH(C_6H_5)_2+H_2O$$

Diphenyl-ethane.

This last reaction permits the preparation of a number of diphenyl-methane derivatives, since, on the one hand, we may use different aldehydes and ketones and, on the other, numerous substitution products of benzene.

Benzophenone, $C_6H_5.CO.C_6H_5$, the ketone corresponding to diphenyl-methane, is formed when the latter is oxidised with chromic acid. This compound and the secondary alcohol *benzhydrol*, $C_6H_5.CHOH.C_6H_5$, have been described on p. 445.

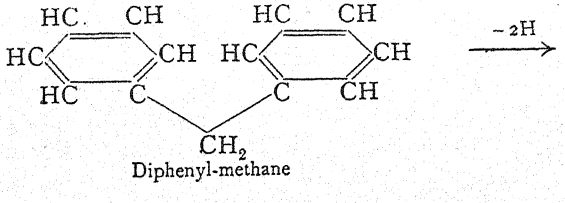
***p*-Diamino-diphenyl-methane,** $CH_2(C_6H_4NH_2)_2$, m.p. 87°, is obtained by heating aniline with *formaldehyde-aniline*, $C_6H_5N:CH_2$ (the condensation product of formaldehyde and aniline). In this reaction intramolecular change occurs.

$$2C_6H_5NH_2+HCHO = H_2N.C_6H_4.CH_2.C_6H_4.NH_2+H_2O$$

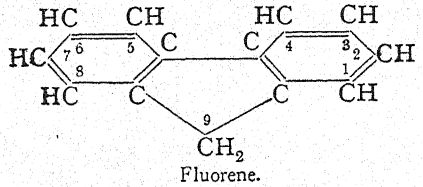
As will be seen later, this process is also used in the technical preparation of *New Fuchsine*.

For ***p*-diamino-benzophenone** and its derivatives see p. 445.

A compound closely related to diphenyl-methane is *diphenylene-methane* or **fluorene,** which is obtained when diphenyl-methane is passed through a tube heated to redness.



Diphenyl-methane



Fluorene.

Fluorene is present in coal tar, and may be obtained from diphenylene ketone or fluorenone (see p. 505) by reduction with zinc dust or with hydriodic acid and phosphorus. It melts at 113°, boils at 295°, and crystallises from alcohol in plates showing a violet fluorescence, from

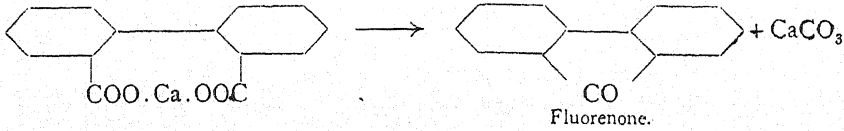
which it takes its name. With picric acid it unites to form a red crystalline picrate, m.p. 81°. *Owing to the arrangement of the double bonds in the molecule,*[1] *the hydrogen atoms of the CH_2-group in fluorene and similarly constituted hydrocarbons are very reactive.*

Thus fluorene condenses with oxalic ester, and with benzaldehyde. In the latter case benzylidene-fluorene, $(C_6H_4)_2C:CH.C_6H_5$, is formed. The acidic nature of the CH_2-group is shown by the interaction of fluorene with caustic potash to give a solid *potassium compound*, $(C_6H_4)_2CHK$. By means of this compound the hydrocarbon can be isolated from coal tar and obtained in the pure state.[2] On energetic oxidation fluorene yields phthalic acid.

The direct preparation of fluorene derivatives from fluorene has been investigated by J. Schmidt,[3] who has shown that the action of concentrated sulphuric acid on the hydrocarbon leads to the formation of 2 : 7-*fluorene-disulphonic acid*, which on fusion with potassium hydroxide gives 2:7:9:9-*tetrahydroxy-fluorene*.

In the *formation of fluorene compounds* three methods are of special value.

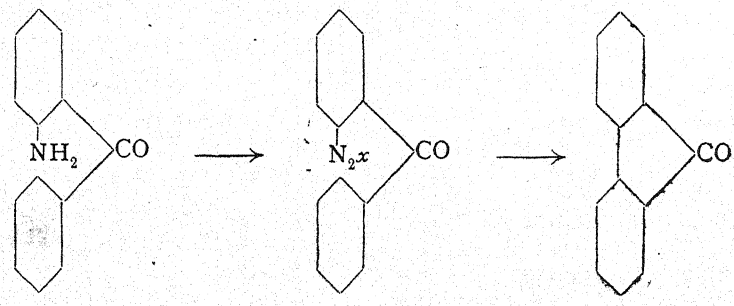
One of these depends on the conversion of appropriate derivatives of diphenic acid into derivatives of fluorenone, by elimination of carbon dioxide, *e.g.* the conversion of diphenic acid itself into fluorenone by the distillation of its calcium salt.



Fluorenone.

This method of preparation establishes the constitution of fluorenone and hence that of fluorene.

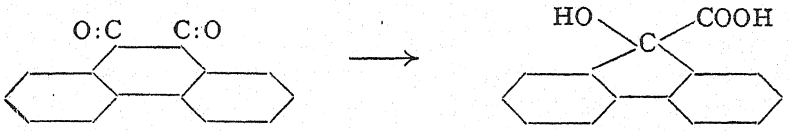
A second method is based on the conversion of *o*-amino-benzophenone into *diphenylene-ketone* by diazotisation and removal of the diazo-group.



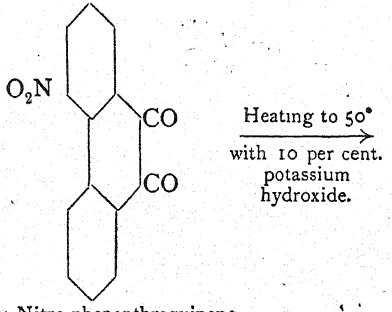
A third process starts from phenanthraquinone and its derivatives, which are described later. When boiled with aqueous alkali, phenanthra-

[1] J. Thiele, *Ber.*, 1900, **33**, 851. *Ann.*, 1906, **347**, 249. W. Wislicenus, *Ber.*, 1900, **33**, 771. [2] Weiszgerber, *Ber.*, 1901, **34**, 1659. Weger and Döring, *Ber.*, 1903, **36**, 878. [3] J. Schmidt and co-workers, *Ann.*, 1909, **370**, 1; 1912, **387**, 147; **390**, 210.

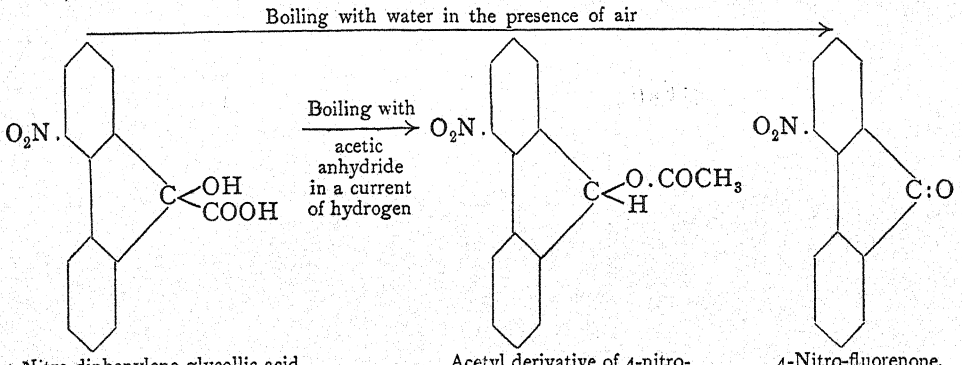
quinone yields *diphenylene-glycollic acid* (9-hydroxy-fluorene-9-carboxylic acid).



Substituted phenanthraquinones undergo a similar reaction to give the corresponding diphenylene-glycollic acids. The latter can then be transformed into other derivatives of fluorene. Most of these glycollic acids, when heated with acetic anhydride in the absence of air, lose carbon dioxide to form the acetyl derivative of the corresponding fluorenyl alcohol; when boiled with acetic anhydride, water, or alkalis, in the presence of air, oxidation occurs simultaneously with the production of a substituted fluorene ketone or fluorenone.[1]



4-Nitro-phenanthraquinone.



4-Nitro-diphenylene-glycollic acid

Acetyl derivative of 4-nitro-fluorenyl alcohol

4-Nitro-fluorenone.

Fluorenone, or diphenylene ketone, is best prepared from fluorene by oxidation with sodium bichromate and glacial acetic acid. It gives the usual reactions of ketones and is a yellow crystalline substance, m.p. 84° and b.p. 341°. On reduction it yields *fluorenyl alcohol*, $(C_6H_4)_2CHOH$, which forms colourless crystals, m.p. 153°.

[1] J. Schmidt and Bauer, *Ber.*, 1905, **38**, 3737.

Hexahydro-fluorene has been isolated from a French gas coal by distillation under reduced pressure, and also by extraction with benzene.[1] It boils at 110° to 120° under 10 mm., and at high temperatures loses hydrogen to form fluorene. This change, which would also be expected to take place with other hydrogenated compounds, may be of general occurrence during the dry distillation of coal under ordinary pressure. It therefore furnishes one, although not the only, explanation of the presence of aromatic hydrocarbons in coal tar, and of hydrogen in coal gas.

III.—TRIPHENYL-METHANE GROUP

This group is of practical as well as theoretical importance. On the one hand it includes a series of widely-used dye-stuffs—the rosanilines, aurines and phthaleins—and on the other it contains compounds which have aroused very great interest in recent years owing to their unexpected properties.

Triphenyl-methane, $(C_6H_5)_3CH$, m.p. 92°, b.p. 358°, the parent substance of the whole group, is obtained by the following reactions.

1. From the magnesium compound of triphenyl-chloro-methane by decomposition with water and acid.[2] This is the most convenient method of preparing the hydrocarbon, since triphenyl-chloro-methane is easily obtained by treating carbon tetrachloride with benzene and aluminium chloride.

$$CCl_4+3HC_6H_5 \xrightarrow{-3HCl} ClC(C_6H_5)_3 \xrightarrow{Mg}$$

Triphenyl-chloro-methane.

$$ClMgC(C_6H_5)_3 \xrightarrow{H_2O} HC(C_6H_5)_3+Cl.Mg.OH$$

2. By the action of aluminium chloride on a mixture of benzal chloride and benzene, or of chloroform and benzene.[3]

$$C_6H_5.CHCl_2+2HC_6H_5 \xrightarrow{-2HCl} (C_6H_5)_3CH \xleftarrow{-3HCl} CHCl_3+3HC_6H_5$$

3. From benzaldehyde and benzene, or benzhydrol and benzene, under the influence of dehydrating agents such as zinc chloride.

$$C_6H_5.CHO+2HC_6H_5 = (C_6H_5)_3CH+H_2O$$

By means of these reactions substituted derivatives of triphenyl-methane may also be prepared. If, for example, in method 3, dimethyl-aniline is used in place of benzene, the leuco-base of malachite green is formed. This important compound is described later.

Triphenyl-methane is a white, crystalline substance, which is insoluble in water and cold alcohol, but readily dissolves in hot alcohol, ether and benzene. From the last it crystallises in union with one molecule of the solvent. When reduced with hydriodic acid and phosphorus it breaks up into benzene and toluene, and with oxidising agents it is converted into triphenyl-carbinol.

[1] A. Pictet and Ramseyer, *Ber.*, 1911, 44, 2486. [2] J. Schmidlin, *Ber.*, 1906, 39, 628; 1912, 45, 3188. [3] For the mechanism of the latter reaction see Norris and Lead, *Am. C. J.*, 1901, 26, 499. Diphenyl-methane, anthracene and diphenylene-phenyl-methane are also formed.

According to Werner,[1] the triphenyl-methyl radical, $(C_6H_5)_3C$, has only a weakened valency bond at its disposal, and consequently the hydrogen atom with which it is united in triphenyl-methane can, under certain circumstances, take part in the formation of molecular compounds. The abnormal nature of the fourth valency of the methane carbon atom is also revealed, in the existence of the free triphenyl-methyl radical, as a yellow strongly unsaturated substance (see p. 520).

Triphenyl-methane and its analogues are characterised by their ability to form molecular addition compounds, *e.g.*,

$(C_6H_5)_3CH+C_6H_6$ (Benzene) $\qquad$ $(C_6H_5)_3CH+C_4H_4S$ (Thiophene)

$(C_6H_5)_3CH+C_4H_4:NH$ (Pyrrole) $\qquad$ $(C_6H_5)_3CH+C_6H_5.NH_2$ (Aniline).

Substitution products of triphenyl-methane may be classified according to whether substitution has occurred in the methane residue, in the phenyl groups, or in both.

Potassium triphenyl-methane, $(C_6H_5)_3CK$, is obtained by heating the hydrocarbon with potassium.

Triphenyl-chloro-methane, $(C_6H_5)_3CCl$, m.p. 111°, may be synthesised from carbon tetrachloride and benzene (p. 506) or prepared by treating triphenylmethane with chlorine. The chlorine atom in this compound is very mobile and easily detached. With water, for example, hydrolysis occurs slowly in the cold and immediately on boiling, to form triphenyl-carbinol and hydrochloric acid. With alcohol it reacts readily to give the *ethyl ether of triphenyl-carbinol*, m.p. 78°.

$$(C_6H_5)_3C.Cl+H_2O = (C_6H_5)_3C.OH+HCl$$
$$(C_6H_5)_3CCl+HO.C_2H_5 = (C_6H_5)_3C.OC_2H_5+HCl$$

It has been shown that the halogen atom of triphenyl-chloro-methane and similar halogen compounds possesses the power of attaching inorganic halides and other components to form highly coloured complexes,[2] such as $(C_6H_5)_3CCl.AlCl_3$, $(C_6H_5)_3CCl.SnCl_4$, $2(C_6H_5)_3CCl.(HgCl_2)_3$. This peculiarity led Werner to the above assumption, that the three phenyl groups make such a demand on the affinity of the methane carbon atom that only a small surplus is left at the disposal of the fourth valency bond.

Triphenyl-Carbinol and the Basic Properties of Carbon

Triphenyl-carbinol, $(C_6H_5)_3C.OH$, m.p. 163°, is readily prepared by the action of phenyl magnesium bromide on methyl benzoate or benzophenone.[3] The experimental investigation of this compound has been of great interest in connection with the hypothesis of the basic character of carbon. *In its chemical behaviour triphenyl-carbinol is a weak base.* When treated in ethereal or benzene solution with dry hydrochloric acid gas, it is quantitatively converted into *triphenyl-chloro-methane*. The latter readily undergoes double decomposition with various

[1] A. Werner, *Ber.*, 1906, **39**, 1278. [2] See also *J. pr. Ch.*, 1921 (2), **103**, 1. [3] Ullmann, *Ber.*, 1903, **36**, 406. Acree, *Ber.*, 1904, **37**, 2755.

silver salts, *e.g.* with silver chromate it forms yellowish-red *triphenyl methyl chromate*, $[(C_6H_5)_3C]_2CrO_4$.

By replacing the phenyl groups in triphenyl-carbinol with methoxyphenyl groups, and especially with *p*-methoxyphenyl (anisyl) groups, Baeyer and Villiger succeeded in obtaining more strongly basic compounds which gave crystalline, highly-coloured salts even with dilute acids. It was found that the effect depended largely on the position of the methoxyl group in the benzene ring, the increase of basicity being greatest in the *p*- and least in the *m*-position.[1]

Salts of this type containing basic carbon are known as *carbonium salts*. As will be shown later, the study of the salts of triphenyl-carbinol and its substitution products has an immediate bearing on the constitution of triphenyl-methane dye-stuffs.

Triphenyl-carbinol not only possesses basic properties but its hydroxyl group is also chemically active in other ways, and can for example be directly replaced by alkoxyl groups. The other reactions of this compound, so far as they are known, appear to place it in an intermediate position between the alcohols and the acids in character, as may be seen from the following summary of its properties.

Triphenyl-carbinol extremely readily forms alkyl ethers with alcohols in the presence of hydrogen chloride; alkalis, on the contrary, do not affect it. The ethyl ether is easily hydrolysed with dilute acids, but quite resistant towards alkalis. With zinc and glacial acetic acid the carbinol is readily reduced to triphenyl-methane. Its acetyl derivative, on being crystallised from alcohol, is converted quantitatively into the ethyl ether, and this with acetic anhydride or acetyl chloride again yields the acetyl compound. The carbinol itself can be acetylated with acetyl chloride, but not with acetic anhydride.

It has been shown by Walden that triphenyl-carbinol is a relatively good electrolyte. Triphenyl-methyl chloride and bromide conduct electricity even better, giving values approximating to those of the quaternary ammonium salts.

Another derivative of triphenyl-methane in which the substituent is in the methine group is **triphenyl-acetic acid**, $(C_6H_5)_3C.COOH$. This is readily obtained [2] from the magnesium compound of triphenyl-methyl chloride by the action of dry carbon dioxide, followed by treatment with water and acids. It crystallises from glacial acetic acid in prisms, m.p. 263° to 264°.

Of the **diphenyl-tolyl-methanes**, $(C_6H_5)_2CH.C_6H_4.CH_3$, in which substitution is in the benzene ring, the *m*-tolyl compound, m.p. 59°, having the methyl group in the meta-position to the methine carbon atom, has been prepared from leucaniline (see next section) by diazotisation and elimination of the diazo-groups. The *diphenyl-tolyl-carbinols*,

[1] Baeyer and Villiger, *Ber.*, 1902, **35**, 3020. [2] J. Schmidlin, *Ber.*, 1906, **39**, 634. See, however, Gilman and Zoellner, *J. Am. C. S.*, 1929, **51**, 3493. H. G. Rule and J. Bain, *J. C. S.*, 1930, 1901.

which can be converted into the hydrocarbons by reduction, may readily be synthesised by means of Grignard's reaction.[1] *Diphenyl*-p-*tolyl-carbinol* was obtained in this manner from phenyl magnesium bromide and the methyl ester of *p*-toluic acid.

Constitution of Carbonium Salts

The *sulphates*,[2] *nitrates* and *perchlorates* of triaryl-methyls are without exception coloured in the crystalline state, and give in general coloured solutions. Some solvents, *e.g.* ether, form colourless solutions. In the coloured solutions and in the crystalline condition the compounds are present as true salts ; in colourless solutions they exist as esters.

The solid triarylmethyl *halides* are colourless, but form both colourless and coloured solutions. In the latter an equilibrium exists between the two forms, as has been clearly shown by the optical investigations of Dilthey.[3] Since the colourless chloride dissolves in strongly dissociating solvents to give a yellow solution which conducts electricity, it has been concluded that this compound also can exist in two modifications, one of which is colourless and unionised, and the other coloured and ionised.

Baeyer proposed to describe ammonium, phosphonium, sulphonium, iodonium, oxonium and carbonium compounds as derivatives of *onium bases*.

For the formulæ derived for dye-stuffs of the triphenyl-methane series from the above standpoint see Baeyer, *Ber.*, 1905, **38**, 569.

A new conception of carbonium salts, based on their remarkable property of ionisation and general similarity to all other *onium* salts, has recently been advanced by Hantzsch.[4] *Onium* halide salts derived from the elements nitrogen, phosphorus, oxygen and sulphur have been shown by Hantzsch to exist in two " chromo-isomeric " series, viz., true colourless halide salts of the complex formulæ $(NR_4)X$, $(OR_3)X$, etc., containing an indirect ionogenic or ionising linking of the halogen, and coloured pseudo-salts of the type $X.N \vdots R_4$, $X.O \vdots R_3$, etc., so far only known in the case of iodides and bromides, containing a direct non-ionogenic union of the halogen. According to this view there are also two isomeric series of carbonium salts :

1. Yellow triphenyl carbonium halides or true salts.
2. Colourless triphenyl-methyl halides or pseudo-salts.

On this hypothesis the carbon derivatives differ from those of N, P, O and S in that the true carbonium salts are coloured, whereas among the other *onium* compounds the pseudo-salts are the coloured forms.

The close analogy between the two series of halide salts, $(C_6H_5)_3CX$, and the isomeric series of ammonium and oxonium halides is traced to a similarity in constitution. Oxonium pseudo-salts, for example, are

[1] Cf. *Ber.*, 1904, **37**, 656, 663, 1245. Also Acree, *ibid.*, 990. [2] Norris and Sanders, *Am. C. J.*, 1901, **25**, 54. [3] W. Dilthey, *J. pr. Ch.*, 1925 [2], **109**, 273. [4] A. Hantzsch, *Ber.*, 1921, **54**, 2573 ; 1930, **63**, 1181. H. E. Fierz, *Helv. Chim. Acta*, 1921, **1**, 221 ; *Ber.*, 1922, **55**, 429, 2043. K. Brand, *J. pr. Ch.*, 1925 [2], **109**, 28.

regarded as normal derivatives of tetravalent oxygen (formula I), with halogen directly attached to oxygen. The true oxonium halides, on the other hand, are complex salts in which oxygen functions as the central atom, the halogen being in ionic union (*i.e.* indirect), with the -onium complex, and therefore in the outer sphere according to Werner's theory (II). Similarly, only the genuine triphenyl-methyl halides are derivatives of structurally normal tetravalent carbon, and owing to the direct linking of the halogens they are non-electrolytes and therefore pseudo-carbonium salts (III). The true triphenyl carbonium salts are electrolytes and must be considered to be complex salts analogous to the true oxonium salts. In these compounds the methane carbon functions as the central atom and is only directly united to the three phenyl groups, thus forming the complex cation; the halogen or acidic radical is situated in the outer sphere, and is in indirect or ionogenic union (IV):

Pseudo salts I. $R.\dot{O}(R).X$ III. $C_6H_5.\dot{C}(C_6H_5)_2.X$

True salts II. $\left(R.O\begin{smallmatrix}R\\R\end{smallmatrix}\right)X$ IV. $\left(C_6H_5.C\begin{smallmatrix}C_6H_5\\C_6H_5\end{smallmatrix}\right)X$

The theory of carbonium salts may be summarised as follows. Tetravalent carbon resembles tetravalent oxygen and sulphur in its ability to function in the cation of an *onium* salt when linked directly to three hydrocarbon radicals. Pseudo-salts built up from a group of this kind and an acidic atom or complex may undergo rearrangement in such a manner that the acidic group changes to indirect union in the outer sphere, and in this state functions as an anion. The complex formula for triphenyl carbonium salts, $[C : Ar_3]\,X$, given above, is supported by data for optical absorption and electrical conductivity, as well as by a number of purely chemical reactions.

Triphenyl-methane Dye-stuffs

From the colourless hydrocarbon, triphenyl-methane, the leuco-compounds of dye-stuffs may be derived by replacing hydrogen in the benzene nuclei by certain chromophoric groups of atoms. Chief among the latter are the amino-group, in which hydrogen may also be substituted by alkyl radicals, and the hydroxyl group. In addition to the derivatives discussed on p. 454, in connection with phthalic anhydride, we have the two following series:

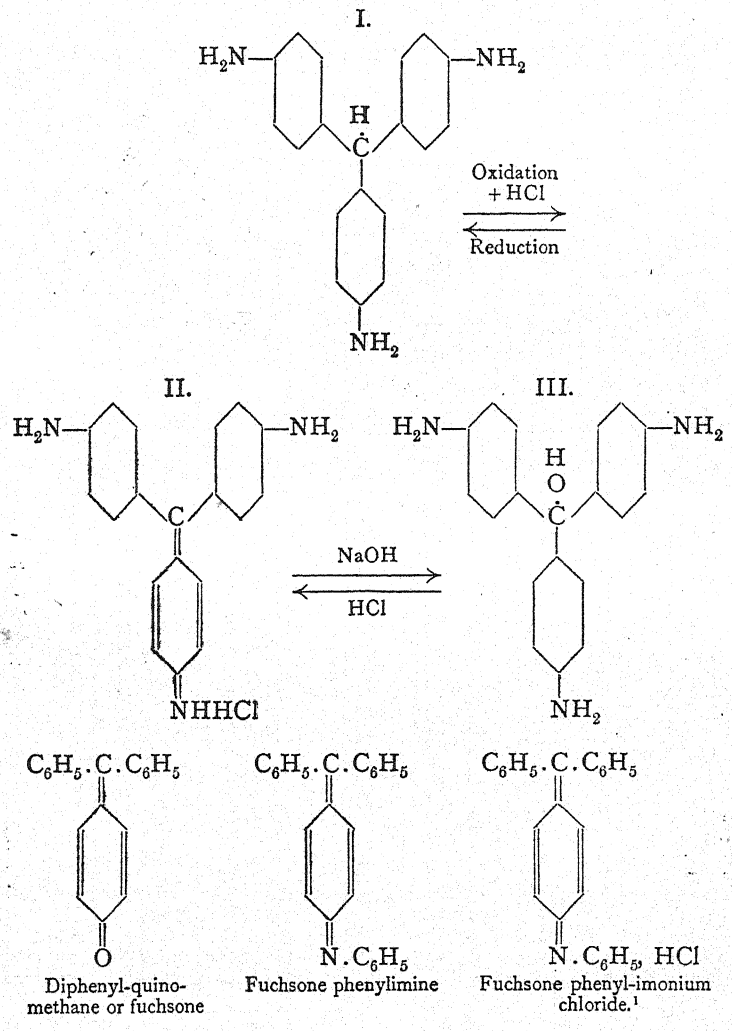
1. The Rosaniline group, derived from amino-triphenyl-methane.
2. The Aurine group, derived from hydroxy-triphenyl-methane.

Constitution of the Triphenyl-methane Dye-stuffs.—The relationship of these compounds to triphenyl-methane, which is discussed below, was first shown in 1878 by *E.* and *O. Fischer*. Since then the greatest advance on the theoretical side has been the introduction of the quinonoid formula

by *Nietzki*, but opinions as to the finer structural details are almost as numerous as the researches on the di- and triphenyl-methane dye-stuffs themselves.

If three amino-groups are introduced into the three benzene nuclei of triphenyl-methane, in the *p*-positions to the methine group, a compound of the structure I is obtained, known as *p*-triamino-triphenyl-methane, or more commonly as *para-leucaniline*.

Leuco-bases or **leuco-compounds** are the colourless compounds obtained by the reduction of dye-stuffs. On oxidation they are again converted into dye-stuffs. The use of these terms is not limited to the triphenyl-methane series, but is common to the indigo and other groups of dyes.

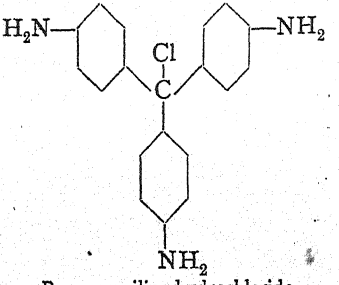


[1] Imonium indicates a compound of the ammonium type, in which a double C-linking (imino-group) is also present.

When *p*-triamino-triphenyl-methane is treated with oxidising agents, a dye-base is obtained which is only stable in the form of its salts, *e.g.* as the hydrochloride *pararosaniline hydrochloride* (II). On being liberated from its salts the free base changes more or less rapidly into colourless *triamino-triphenyl-carbinol* (III). Since the dye-stuffs are in many ways similar to the quinonimine dyes, they are considered by most chemists to possess the quinonoid structure, as represented in formula II.

Stable forms of this type of colour base have been discovered [1] among phenyl quinonimine derivatives by Baeyer and Villiger. The parent substance of this group of compounds may be considered to be diphenyl-quino-methane, for which the name *fuchsone* has been suggested, thus enabling members of this group to be named systematically.

The probability of the quinonoid formula, as applied to salts of triphenyl-methane dyes, has been considerably strengthened by recent research,[2] and this formulation will be adopted in the following pages. For a long time, however, the structure suggested in 1880 by Rosenstiehl, representing the salts as esters of a carbinol (see formula below), was regarded as being as probable as the quinone formula and was supported by the work of Baeyer.[3]



Para-rosaniline hydrochloride
or para-fuchsine
(*Rosenstiehl's formula*).

It must be admitted that the newer conceptions, which are more or less based upon the older Rosenstiehl formula, can be supported by a considerable body of evidence. According to Fierz, Dilthey and others [4] the triaryl-methylium salts $[Ar_3C]X$ discussed on pp. 509 and 510 are to be regarded as the chromogens, from which dye-stuffs of the triphenyl-methane series are derived by the replacement of hydrogen atoms by auxochrome groups, such as OH, NH_2, NMe_2, etc.

[1] Baeyer and Villiger (*Ber.*, 1904, **37**, 597, 2848) obtained the quinonoid anhydride of *p*-amino-triphenyl-carbinol, *fuchsonimine*, $\left[\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!\!>C=C_6H_4=NH\right]_2$, in a colourless, crystalline dimolecular state by the interaction of phenyl magnesium bromide and *p*-amino-benzophenone. Many of the triphenyl-methane colour bases exist in two forms, a colourless carbinol and a coloured quinonoid modification. Baeyer and Villiger, 1902, **35**, 715. Noelting and Philipp, *Ber.*, 1908, **41**, 579. [2] *Cf.* Wieland, Popper and Seefried, *Ber.*, 1922, **55**, 1816. [3] Baeyer, *Ber.*, 1906, **38**, 569. [4] H. Fierz and H. Koechlin, *Helv. Chim. Acta*, 1919, I, 210; W. Dilthey, *J. pr. Ch.*, 1925 [2], **109**, 273; W. Madelung, *J. pr. Ch.* [2], 1926, **111**, 100; K. Brand, *ibid.*, 1925, **109**, 28; R. Wizinger, *Ber.*, 1927, **60**, 1377.

The nature of the colour bases of triphenyl-methane dye-stuffs will be discussed more fully at the end of this chapter.

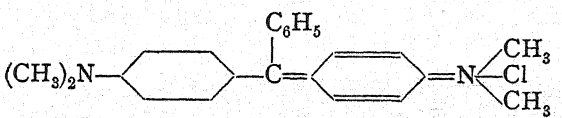
1. Rosaniline Dye-stuffs

Malachite green, *Victoria green.* When benzaldehyde is heated on the water-bath with dimethylaniline in the presence of condensing agents such as hydrochloric acid, sulphuric acid or zinc chloride, there is formed tetramethyl-di-*p*-amino-triphenyl-methane or *leuco-malachite green.* In this reaction the hydrogen atoms in the *p*-position to the $N(CH_3)_2$ groups unite with the aldehydic oxygen atom, with elimination of water. The leuco-base is obtained in colourless leaflets or prisms.

$$C_6H_5.CHO + \begin{matrix} H.C_6H_4.N(CH_3)_2 \\ H.C_6H_4.N(CH_3)_2 \end{matrix} = C_6H_5{-}CH\begin{matrix} C_6H_4.N(CH_3)_2 \\ C_6H_4.N(CH_3)_2 \end{matrix} + H_2O$$

Leuco-base of malachite green.

When the hydrochloride of the leuco-base is oxidised, malachite green is obtained. This is usually carried out in dilute solution by means of lead peroxide in the presence of a little acetic acid.



Quinonoid formula for malachite green.

The compound is most conveniently isolated from solution in the form of the zinc double salt, $3(C_{23}H_{25}N_2Cl)$, $2ZnCl_2$, H_2O, by precipitation with zinc chloride and common salt, or the carbinol base may be precipitated with sodium carbonate, and converted into the oxalate by treatment with oxalic acid.

The zinc double salt or the oxalate is placed on the market in the form of green crystals having a metallic sheen. Malachite green dyes wool, silk, jute, leather and tannined cotton a green colour, which is not very fast to light.

Tetramethyl-diamino-triphenyl-carbinol,

$$C_6H_5.C(OH)\begin{matrix} C_6H_4N(CH_3)_2 \\ C_6H_4N(CH_3)_2 \end{matrix}$$

is produced by the action of alkalis on malachite green. It may be synthesised by the interaction of 2 mols. of dimethylamino-phenyl magnesium bromide with 1 mol. benzoic ester, and forms colourless crystals, m.p. 132°.

Among the various dyes of this type used in industry the following may be mentioned.[1]

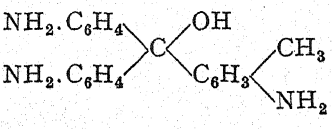
[1] For the influence of substitution on the colour of malachite green see Noelting and Gerlinger *Ber.*, 1906, **39**, 2041.

Brilliant green, *Guignet's green,* is the ethyl compound corresponding to malachite green, obtained by condensing diethylaniline with benzaldehyde.

Patent blue, an *o,p*-disulphonic acid of this group, is prepared by condensing *m*-nitrobenzaldehyde with diethylaniline, replacing NO_2 by OH by way of the diazo-compound, followed by sulphonation and oxidation. It is an important dye-stuff which dyes wool a very fast greenish-blue colour and is stable towards alkali.

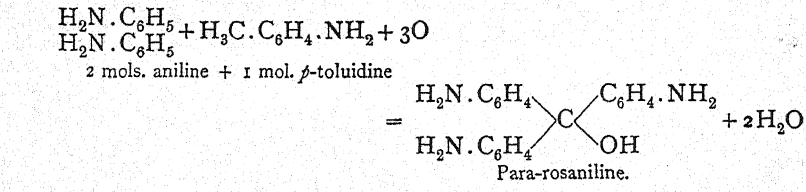
Triamino-triphenyl-carbinols and their Derivatives

The true rosaniline dye-stuffs are derived from p_3-triamino-triphenyl-carbinol (formula III, p. 511) and p_3-triamino-diphenyl-*m*-tolyl-carbinol.



When treated with an equivalent of hydrochloric or acetic acid these compounds lose a molecule of water and form salts of the type illustrated on p. 511, which are valuable dyes. Owing to their preparation from crude *p*-toluidine, the dyes derived from p_3-triamino-triphenyl carbinol were originally distinguished as para-compounds (*e.g.* para-rosaniline, para-rosolic acid), and this inconvenient nomenclature is still in use.

Para-rosaniline, $C_{19}H_{19}N_3O$ (constitution, see p. 510), is prepared by oxidising a mixture of *p*-toluidine (1 mol.) and aniline (2 mols.). Among the numerous oxidising agents available for this purpose arsenic acid (the older process) or nitrobenzene is generally used. It is supposed that the methyl group of *p*-toluidine is first oxidised to the aldehyde stage, and the *p*-amino-benzaldehyde so formed condenses with aniline as in the malachite green preparation (p. 513). Hence the "methane carbon atom" of para-rosaniline has its origin in the methyl group of *p*-toluidine.[1]



2 mols. aniline + 1 mol. *p*-toluidine

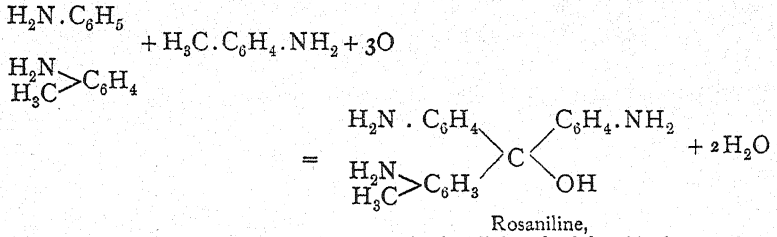
Para-rosaniline.

The colourless carbinol base—which is triacidic and more strongly basic than ammonia—unites with one equivalent of an acid with loss of water to form red dyes. Simultaneously the molecule undergoes rearrangement into the quinonoid structure (possibly, however, the carbinol ester type persists, see pp. 511 and 512). Hydrochloric acid yields para-

[1] On examining this reaction it is clear that pure aniline alone can yield neither para-rosaniline nor rosaniline on oxidation (it actually gives products of the induline type). In this case the group required for the formation of the "methane carbon" is wanting.

rosaniline hydrochloride or **para-fuchsine,** which is a constituent of technical fuchsine. On reduction with zinc dust and hydrochloric acid this salt is converted into *para-leucaniline* or p-*triamino-triphenyl-methane* (colourless needles, m.p. 148°), from which para-rosaniline is easily regenerated by oxidation.

Rosaniline, $C_{20}H_{21}N_3O$, is a homologue of para-rosaniline and is obtained by the above condensation when 1 mol. aniline is replaced by 1 mol. *o*-toluidine, *i.e.*, when an equimolecular mixture of aniline, *o*-toluidine and *p*-toluidine is oxidised. The additional methyl group is therefore situated in the *o*-position to an amino group.

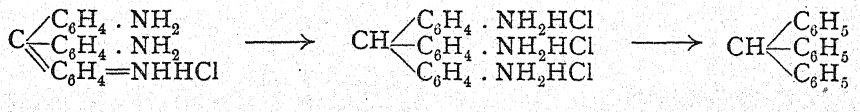


Rosaniline,
triamino-diphenyl-tolyl-carbinol.

Rosaniline, like para-rosaniline, is a colourless triacidic base, which unites with one equivalent of an acid to form coloured salts of the colour base, a molecule of water being set free. The salt containing one molecular proportion of hydrochloric acid is known as **fuchsine** or **magenta.** In the solid state this consists of green crystals with a metallic lustre. It dissolves in water, giving a deep reddish-purple colour. The solution dyes silk and wool directly, and cotton after having been mordanted with tannin and potassium hydrogen tartrate. But the red colours so obtained are not fast to light. On reduction, rosaniline gives *leucaniline*, $\begin{matrix}NH_2\\CH_3\end{matrix}\!\!>\!C_6H_3\!-\!CH(C_6H_4.NH_2)_2$, m.p. 100°.

Rosaniline also forms acid salts such as $C_{20}H_{20}N_3Cl+2HCl$, which gives a yellowish-brown solution. On the addition of much water these dissociate into the neutral salts and free acid.

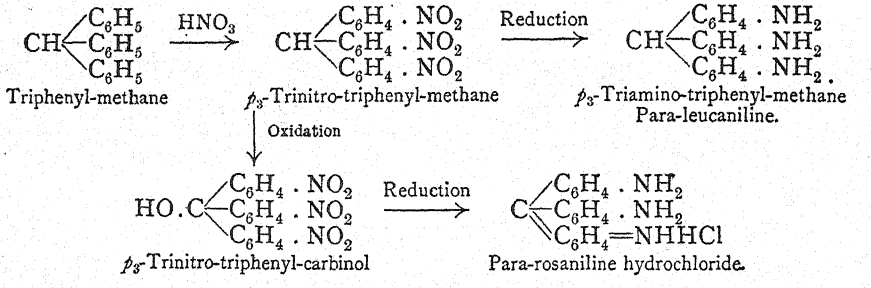
The relationship of para-fuchsine and fuchsine to triphenyl-methane was explained in 1878 by E. and O. Fischer.[1] Para-fuchsine (para-rosaniline hydrochloride) was reduced to the hydrochloride of para-leucaniline, and the latter converted by way of the diazonium salt into triphenyl-methane :



In addition, triphenyl-methane was synthesised from benzene and chloroform in the presence of aluminium chloride, and converted by

[1] *Ann.*, **194**, 242. E. Fischer and Jennings, *Ber.*, 1893, **26**, 2220.

nitration into p_3-trinitro-triphenyl-methane, from which para-leucaniline and para-rosaniline were obtained as follows :—



The first series of changes was also carried through with rosaniline, yielding *m*-tolyl-diphenyl-methane.

Finally, the assumption that the three amino-groups in rosaniline and para-rosaniline occupied the para-positions was also proved beyond doubt by other reactions.

Nuclear-substituted Fuchsines

In addition to the methods described above, a number of other processes for the preparation of fuchsine dye-stuffs have been developed. One of these involves the condensation of formaldehyde with aniline to give formaldehyde-aniline, $C_6H_5—N=CH_2$, which on further treatment with aniline is converted with intramolecular rearrangement into diamino-diphenyl-methane (p. 503). When this base is heated with aniline and an oxidising agent (nitrobenzene) a hydrogen atom of the CH_2-group is replaced by an aminophenyl group, with the production of para-fuchsine. By employing substituted anilines in place of aniline itself this method may be used for the preparation of substituted fuchsines.

New Fuchsine, $C_{22}H_{23}N_3HCl$, containing three *o*-toluidine groups in place of the three aniline residues, is very readily obtained in the above way. It dyes a bluish-red and is more soluble in water than fuchsine.

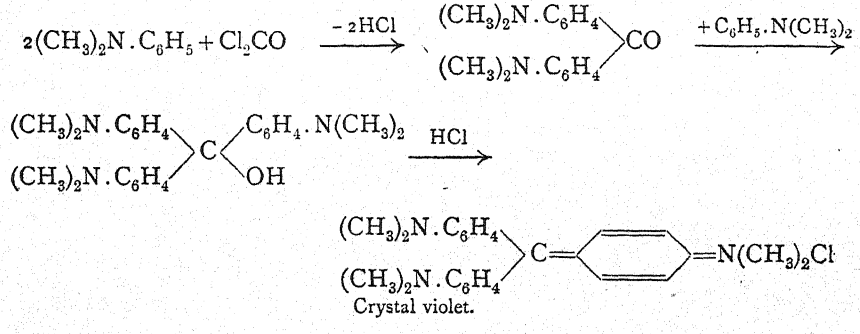
Acid Fuchsine, *acid magenta*, $C_{20}H_{17}N_3(SO_2.ONa)_2$, is a disulphonic derivative of fuchsine, prepared by heating rosaniline with fuming sulphuric acid at 120°. It dyes wool and silk in weak acid bath, thus enabling fuchsine to be used as an acid dye.

Methylated and Phenylated Derivatives

When the hydrogen atoms of the NH_2-groups in rosaniline and para-rosaniline are replaced by methyl or ethyl groups, the red colour of the dye is changed to violet. The tendency towards blue becomes more pronounced as the number of alkyl groups increases. At first these compounds were obtained by alkylating rosaniline with the aid of methyl or ethyl iodide, and later by use of methyl alcohol and hydrochloric acid in place of the more expensive methyl iodide. Recently dimethyl-aniline

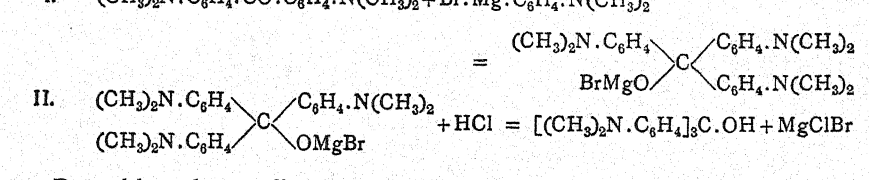
(prepared by heating aniline with methyl alcohol and hydrochloric or sulphuric acid at 200°) has been used as starting material and oxidised directly to alkylated para-rosanilines, usually by means of cupric salts. In this manner **methyl violet** is obtained, consisting of a variable mixture of the hydrochlorides of tetra-, penta- and hexamethyl para-rosanilines. It is an iridescent green resinous mass, which dissolves in water to give a beautiful violet solution. If hydrogen is substituted by benzyl groups ($C_6H_5.CH_2$—), instead of methyl groups, a bluer shade is obtained (*benzyl violet*).

Crystal violet is the hydrochloride of pure hexamethyl para-rosaniline. It is prepared by the interaction of phosgene and dimethyl-aniline to form tetramethyl-diamino-benzophenone (Michler's ketone, p. 445), and condensing the latter with dimethyl-aniline in the presence of phosphorus chloride or aluminium chloride. It crystallises exceedingly well.



Crystal violet.

An interesting method of forming crystal violet is as follows (*Ber.*, **36**, 4296): On mixing an ethereal solution of dimethylamino-phenyl magnesium bromide with an ethereal solution of Michler's ketone, a yellowish-brown precipitate of the additive magnesium compound is first obtained (equation I). On acidification with hydrochloric acid this yields hexamethyl-triamino-triphenyl-carbinol (equation II) which changes into the hydrochloride of crystal violet.

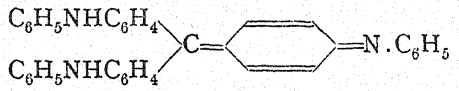


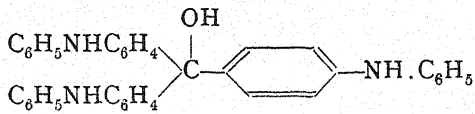
Pure blue dye-stuffs may be obtained from rosaniline by replacing the amino-hydrogen atoms by phenyl or naphthyl groups.

Aniline blue, *triphenyl-para-rosaniline hydrochloride*, is prepared by heating rosaniline with a large excess of toluidine-free aniline and benzoic acid to 180°, when ammonia is liberated. On treating the product with hydrochloric acid the dye crystallises out. It can also be obtained by the oxidation of diphenylamine. The dye is very sparingly soluble in water, but more soluble in alcohol; hence it is sometimes termed "spirit blue." Sulphonic derivatives of this compound are soluble in water and

are more often used than the parent substance. The sodium salt of the monosulphonic acid, known as **alkali blue,** is used especially for dyeing wool, and the sodium salts of the di- and trisulphonic acids, **water blue,** for dyeing cotton.

Diphenylaminofuchsone-phenylimine, the imine base of aniline blue (formula I), has been prepared by heating trianisyl-carbinol with benzoic acid and aniline, and subsequently decomposing the benzoate of the dye with sodium hydroxide under special conditions.[1] The compound is a black crystalline powder, m.p. 237° to 238°, which readily adds on water to form triphenyl-para-rosaniline (formula II). On reduction it yields the leuco-base, and with acids gives the corresponding dye-salts.

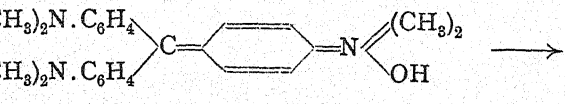
I. 

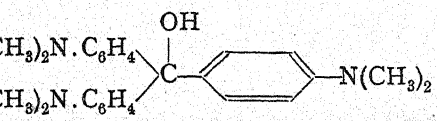
II. 

Constitution of the Rosaniline Dye-bases

The views at present held regarding the constitution of triphenyl-methane salts have already been discussed on pp. 509-512, and the following paragraphs deal with the nature of the dye-*bases* which give rise to the salts. In this connection Hantzsch [2] has drawn a number of conclusions from a physico-chemical examination of the conductivity of the system *dye-salt*+1 *NaOH*.

When crystal violet (the hydrochloride of hexamethyl-triamino-triphenylmethane) is treated in solution with one equivalent of alkali, the coloured solution first obtained is strongly alkaline and conducts the electric current. In time, however, it becomes colourless, and finally the alkalinity vanishes and the conductivity falls. It appears therefore that, immediately after the addition of an equivalent of alkali to crystal violet, the actual base of structure (*a*) is present in solution, and that this slowly isomerises to the dye-base (pseudo-base) of formula (*b*).

(*a*) 

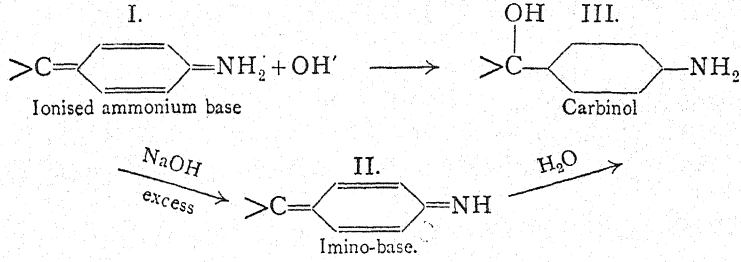
(*b*) 

Similar results are obtained with other bases of triphenyl-methane

[1] Baeyer and Villiger, *Ber.*, 1904, **37**, 2870. [2] Hantzsch, *Ber.*, 1900, **33**, 278, 752; *Ber.*, 1904, **37**, 3434.

dye-stuffs, and the conclusions arrived at by Hantzsch may be summarised as follows :

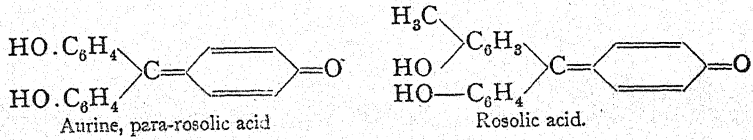
The true primary bases of the dye-salts of this series are ammonium hydroxide derivatives of the same colour as the salts. They cannot be isolated in the solid state but exist only in dilute aqueous solution, *i.e.*, in the almost completely ionised condition [1] (formula I).



Even in the dissociated state these dye-bases slowly undergo molecular rearrangement with variable but always measurable velocity to form the pseudo-bases or carbinols (formula III). When the salt of a dye-base such as fuchsine, which still contains hydrogen attached to nitrogen, is treated in aqueous solution with *excess* of sodium hydroxide, an anhydro-base of different colour is precipitated (formula II). This can be extracted with indifferent solvents. Fuchsine, for example, yields a brown compound known as *Homolka's base*.[2] These anhydrides are related to the primary dye-bases as ammonia is to ammonium hydrate. The imino-base is therefore not to be considered as the actual base of fuchsine, but rather as its anhydride. With acids it is instantly converted into salts of the dye-base.

2. Aurines, Rosolic Acid Dyes

Compounds of this class possess a constitution similar to that of the true rosaniline dyes, although the nitrogen has been replaced by oxygen groups ; they therefore bear the same relationship to phenol as the rosanilines bear to aniline. Hence they are not basic but weakly acidic dyes, which are, however, of much less value than those of the rosaniline series, since they are difficult to attach to the fabric. They are chiefly employed in the form of lakes in the paper and wall-paper industries. In these compounds the quinonoid structure is assumed so readily—even in the absence of mineral acid—that the corresponding carbinols are unknown.



[1] These formulæ only show that part of the molecule undergoing change. [2] This base was first obtained from fuchsine by Homolka and is formulated according to type II above as $(NH_2C_6H_4)_2C : C_6H_4 : NH$ (Baeyer and Villiger, *Ber.*, 1905, **38**, 579).

Aurine, *para-rosolic acid*, may be obtained in the pure state from para-rosaniline by diazotisation and boiling the diazonium salt with water, when NH_2 is replaced by OH. Technically it is prepared by heating phenol with sulphuric acid and oxalic acid (the latter furnishing the "methane carbon atom"). It forms dark red rhombic crystals or red needles with a greenish lustre, dissolves in alkali to a fuchsine red solution, and has also weakly basic properties since it unites with acids. When heated to 150° with aqueous ammonia it yields para-rosaniline, and with nascent hydrogen it is reduced to *leucaurine*, trihydroxy-triphenyl-methane, $CH(C_6H_4.OH)_3$. The latter is a colourless, crystalline compound which turns red in air or with oxidising agents, owing to the formation of aurine. Trianisyl-carbinol, the trimethyl ether of the carbinol corresponding to aurine, has already been mentioned on p. 508.

Rosolic acid, the quinonoid anhydride of p_3-trihydroxy-diphenyl-*m*-tolyl carbinol (formula, see p. 519), is formed when the diazo-compound of rosaniline is boiled with water, or when a mixture of phenol and cresol is heated with arsenic acid and sulphuric acid (the methyl group of cresol provides the "methane carbon"). It forms crystals of greenish lustre which are insoluble in water and dissolve to a red solution in alkalis. With reducing agents rosolic acid is converted into *leuco-rosolic acid*, trihydroxy - diphenyl - tolylmethane, $(HOC_6H_4)_2CH.C_6H_3(CH_3).OH$. When heated with water, rosolic acid breaks up into *p*-dihydroxyphenyl-tolyl ketone and phenol.

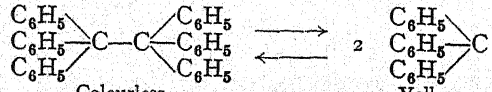
The **phthaleïns,** which may be regarded as carboxy-derivatives of triphenyl-methane, have already been discussed in connection with phthalic anhydride.

Triphenyl-methyl and Trivalent Carbon

The researches of Gomberg [1] on triphenyl-methyl threw a new light on the problem of the valency of carbon (*cf.* p. 14). By treating a benzene solution of triphenyl-methyl chloride with zinc, silver or mercury in an atmosphere of CO_2, Gomberg obtained a yellow solution which on evaporation deposited colourless crystals of **hexaphenyl-ethane.** In the

$$2(C_6H_5)_3C.Cl+Zn = (C_6H_5)_3C.C(C_6H_5)_3+ZnCl_2$$

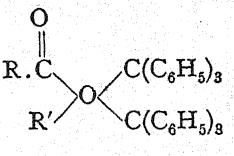
dissolved state the colourless hydrocarbon partially breaks down to yield an equilibrium mixture containing a yellow strongly unsaturated compound, which is formulated as the free radical, **triphenyl-methyl.** On this view of its structure triphenyl-methyl may be regarded as the first compound of trivalent carbon to be discovered.



[1] Gomberg, *J. Am. C. S.*, 1900, **22**, 757; 1901, **25**, 317; 1913, **35**, 446; 1914, **36**, 1144; 1919, **41**, 1655; 1922, 44, 1810; 1923, **45**, 190, 207. See also monograph by J. Schmidlin: *Das Triphenylmethyl*, published by Enke, Stuttgart.

The proportion of triphenyl-methyl present in the equilibrium mixture depends to some extent on the nature of the solvent (in ether it is about 10 per cent.), and also upon the concentration and temperature. Such solutions do not obey Beers Law. Thus the depth of coloration does not diminish proportionally with dilution, but an increase in the latter displaces the equilibrium in favour of the monomolecular triphenyl-methyl, leading to a relative increase in the intensity of colour. A similar effect is brought about by a rise in temperature.

In triphenyl-methyl it appears that the three unsaturated phenyl groups make such a demand on the affinity of the methane carbon atom that its fourth valency is considerably weakened and no longer able to combine readily with a similar weak valency to form hexaphenyl-ethane. An explanation based on the theory of resonance has already been given on p. 91. The trivalent carbon derivative, however, is still strongly unsaturated, as is illustrated by its behaviour towards oxygen and the halogens, as well as by the formation of addition complexes with various classes of organic compounds. When a solution is shaken with air, the yellow colour is immediately discharged, and oxygen is absorbed with production of a *peroxide*, $(C_6H_5)_3C.O.O.C(C_6H_5)_3$, m.p. 185°. If air is then excluded the colour rapidly reappears as more triphenyl-methyl is regenerated by dissociation of some of the remaining hexaphenyl-ethane. A solution of iodine is immediately decolorised by triphenyl-methyl to form *triphenyl-methyl iodide*, $(C_6H_5)_3CI$, m.p. 132°. With ether a crystalline compound of the composition $2(C_6H_5)_3C+(C_2H_5)_2O$ is obtained, in which oxygen appears to be tetravalent. Esters also combine with triphenyl-methyl, giving compounds which probably possess the annexed structure. Ketones, aromatic and unsaturated aliphatic hydrocarbons, etc., also give addition products, that with amylene, for example, having the formula $[(C_6H_5)_3C]_2+C_5H_{10}$. The experimental evidence so far available shows that, when triphenyl-methyl combines with another substance, each valency of the latter which is brought into play invariably takes up one $(C_6H_5)_3C$- complex, regardless of the stability of the resulting product. Amylene and all aromatic hydrocarbons, as well as ethers, esters and ketones, take up in a uniform manner two triphenyl-methyl groups per molecule.



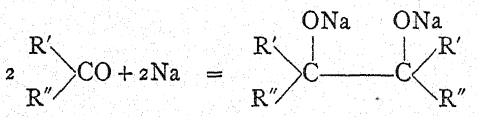
By similar methods a number of analogous compounds have been prepared.[1] One of the most interesting of these is the **tridiphenyl-methyl**, $(C_6H_5.C_6H_4)_3C$, obtained by Schlenk. As has been established by molecular weight determinations, this compound exists only in a purple monomolecular form. Hence the characteristic equilibrium between mono- and di-molecular forms found in the case of triphenyl-methyl does not occur with the tridiphenyl derivative.

[1] Pentaphenyl-ethyl, Schlenk and Mark, *Ber.*, 1922, 55 [*B*], 2285, 2299. For other compounds see Schlenk, *Ann.*, 1909, **368**, 303; **372**, 1. J. Schmidlin, *Ber.*, 1912, **45**, 3171. Schlenk and Bornhardt, *Ber.*, 1913, **46**, 1482.

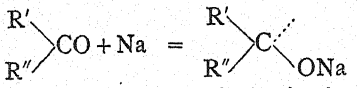
Metallic Ketyls.—Another group of compounds containing trivalent carbon has been discovered by Schlenk in the metallic ketyls,[1] of the general formula shown below. They are formed by the action of alkali metals on ketones, and are characterised by intense colour and great sensitiveness to oxygen. Trivalent carbon thus appears to betray itself in its strong chromophoric influence. In general, the interaction of an alkali metal and a ketone falls into one of the three following classes :

1. Where an enolic form can occur a metallic compound is produced with evolution of hydrogen, as in the case of acetone, which reacts as the enol $CH_2:C(OH).CH_3$.

2. The alkali metal may combine without evolution of hydrogen to form a saturated dimolecular compound :



3. The alkali metal may combine directly to yield a metallic ketyl :



Sodium ketyl

IV.—TETRAPHENYL-METHANE GROUP

Tetraphenyl-methane, $(C_6H_5)_4C$, can be prepared from triphenyl-carbinol. The latter, on heating with aniline hydrochloride, yields the hydrochloride of p-*amino-tetraphenyl-methane*, and from the free base (m.p. 245°) the amino-group is eliminated by the diazo reaction.

$$(C_6H_5)_3C.OH \longrightarrow (C_6H_5)_3C—C_6H_4.NH_2 \longrightarrow (C_6H_5)_3C—C_6H_5$$

It has also been shown by Gomberg [2] that tetraphenyl-methane is readily obtained by the action of phenyl magnesium bromide on triphenyl-methyl chloride :

$$(C_6H_5)_3C.Cl+C_6H_5MgBr = (C_6H_5)_4C+MgBrCl$$

It forms colourless crystals, m.p. 282° and b.p. 431°.

If triphenyl-carbinol is heated with phenol, instead of with aniline, the resulting product is p-*hydroxy-tetraphenyl-methane*, m.p. 282°.

$$C(C_6H_5)_3.OH+C_6H_5OH = C(C_6H_5)_3(C_6H_4.OH)+H_2O$$

V.—DIBENZYL OR DIPHENYL-ETHANE GROUP

Dibenzyl, s-*diphenyl-ethane*, $C_6H_5.CH_2.CH_2.C_6H_5$, can be prepared by the action of copper or sodium on benzyl chloride,

$$C_6H_5CH_2.Cl+2Na+Cl.CH_2C_6H_5 = C_6H_5CH_2.CH_2C_6H_5+2NaCl$$

by the oxidation of toluene with potassium persulphate,

$$2C_6H_5.CH_3+K_2S_2O_8 = C_6H_5.CH_2.CH_2.C_6H_5+K_2SO_4+H_2SO_4$$

[1] Schlenk and Thal, *Ber.*, 1913, **46**, 2840. [2] Gomberg, *Ber.*, 1906, **39**, 1461. Freund, *Ber.*, **39**, 2337.

and by the reduction of stilbene with sodium and alcohol,

$$C_6H_5.CH{:}CH.C_6H_5+2H = C_6H_5.CH_2.CH_2.C_6H_5$$

Dibenzyl forms a glistening white crystalline mass. It melts at 52° and boils at 284°.

Homologues of dibenzyl may be obtained by similar methods, *e.g.* *o*-, *m*- and *p*-xylene on oxidation with potassium persulphate yield o_2-, m_2- and p_2-dimethyl-dibenzyl respectively.

Stilbene, s-*diphenyl-ethylene*, $C_6H_5.CH{:}CH.C_6H_5$, has been known a long time and is formed in a great many reactions. It is best prepared by the interaction of benzaldehyde and benzyl magnesium chloride, the carbinol first produced immediately parting with water.

$$C_6H_5.CH{:}O + Mg\begin{matrix}CH_2.C_6H_5\\Br\end{matrix} \longrightarrow C_6H_5.CH\begin{matrix}CH_2.C_6H_5\\OMgBr\end{matrix} \longrightarrow$$

$$C_6H_5.CH\begin{matrix}CH_2.C_6H_5\\OH\end{matrix} \xrightarrow{-H_2O} C_6H_5.CH{:}CH.C_6H_5$$

By this method a great variety of substituted stilbenes have also been obtained, *e.g.* *α-phenyl-stilbene*, or *triphenyl-ethylene*, $(C_6H_5)_2C{:}CH.C_6H_5$, which melts at 68° and boils at 221° under 14 mm.

Another method of preparing stilbene consists in heating an alkaline solution of phenyl-nitromethane.

$$2C_6H_5.CH{:}NO.ONa = C_6H_5.CH{:}CH.C_6H_5+2NaNO_2$$

This may be much more readily effected by starting from the sodium compound of phenyl-nitro-acetonitrile, which is easily obtained from ethyl nitrate and benzyl cyanide.

$$2C_6H_5C(CN){:}NO.ONa+4NaOH+2H_2O = C_6H_5.CH{:}CH.C_6H_5+2Na_2CO_3+2NH_3+2NaNO_2$$

Stilbene crystallises in lustrous plates or prisms, m.p. 124° and b.p. 306°. It yields dibenzyl on reduction, and readily adds on halogens and hydrogen halides, *e.g.* with bromine it forms stilbene dibromide, $C_6H_5.CHBr.CHBr.C_6H_5$.

***p*-Nitrostilbene** is produced by the interaction of benzaldehyde and nitrophenyl-acetic acid in the presence of piperidine.[1]

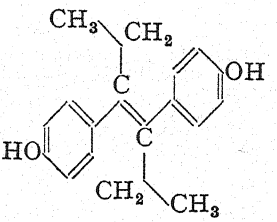
$$C_6H_5.CHO+H_2C(COOH).C_6H_4.NO_2 \rightarrow C_6H_5.CH{:}C(COOH).C_6H_4.NO_2 \rightarrow C_6H_5.CH{:}CH.C_6H_4.NO_2$$

It forms yellow needles, m.p. 155° and exists also in a labile modification,[2] m.p. 64°. With stannous chloride it is easily reduced to colourless ***p*-amino-stilbene.**

4:4′-Diamino-stilbene, $NH_2.C_6H_4.CH{:}CH.C_6H_4.NH_2$, and its disulphonic acid are used in the preparation of substantive azo-dyes. They are obtained from *p*-nitrotoluene or its sulphonic acid. When *p*-nitrotoluene sulphonic acid is boiled with sodium hydroxide it yields

[1] P. Pfeiffer and Sergiewskaja, *Ber.*, 1911, 44, 1107. For stilbene *o*-carboxylic acids see Pfeiffer and Matton, *ibid.*, p. 1113. [2] R. Stoermer and Oehlert, *Ber.*, 1922, 55, 1232.

p-azoxy-stilbene disulphonic acid, from which on reduction with zinc dust and alkali is obtained diamino-stilbene disulphonic acid.



***trans*-Diethyl-stilboestrol** is one of the most potent œstrogens known,[1] and is employed as such in medicine (*stilbœstrol*, see inset formula).

Tolane, *diphenyl-acetylene*, $C_6H_5.C{\equiv}C.C_6H_5$, is prepared from the above-mentioned stilbene dibromide by boiling with alcoholic potash. Tolane unites with two or four atoms of halogen and also with nitrogen peroxide. It melts at 60°.

$$C_6H_5.CHBr.CHBr.C_6H_5+2KOH = C_6H_5.C:C.C_6H_5+2KBr+2H_2O$$

Certain alcoholic and ketonic derivatives of dibenzyl are of interest.

Benzoin, a keto-alcohol of dibenzyl, is formed when benzaldehyde is warmed in alcoholic solution with potassium cyanide. The mechanism of the condensation is not yet understood.[2]

$$2C_6H_5CHO = C_6H_5.CO.CHOH.C_6H_5$$
Benzoin.

This reaction is a general one, and may be carried out with other aldehydes of the same type as benzaldehyde. It is also reversible and by use of two different aromatic aldehydes mixed benzoins may be formed.[3]

Benzoin crystallises in colourless, odourless prisms, m.p. 137°. It reacts both as a ketone and as a secondary alcohol. Thus it yields an oxime and an osazone, and also ethers and esters. On reduction with sodium amalgam hydrobenzoin is formed.

$$C_6H_5.\overset{O}{\overset{\|}{C}}{-}\overset{OH}{\overset{|}{C}}H.C_6H_5+2H = C_6H_5.\overset{OH}{\overset{|}{C}}H{-}\overset{OH}{\overset{|}{C}}H.C_6H_5$$
Hydrobenzoin.

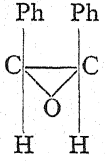
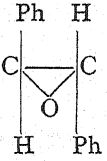
Benzoin contains an asymmetric carbon atom and has been synthesised in *d*- and *l*-forms by McKenzie and Wren.[4]

Hydrobenzoin, s-*diphenyl-glycol*, is prepared as described above, or by the direct reduction of benzaldehyde by chemical or electrolytic methods. It is also obtained from stilbene dibromide, $C_6H_5.CHBr.CHBr.C_6H_5$, by treatment with potassium acetate or silver acetate and hydrolysis of the resulting diacetyl ester. It contains two similar asymmetric carbon atoms and thus exhibits the same type of isomerism as tartaric acid. The reactions already quoted actually yield a variable mixture of the two inactive forms, *hydrobenzoin*, m.p. 134°, and *isohydrobenzoin*, m.p. 119°. Of these, the former is a meso-compound, whereas the latter is racemic [5] and can be resolved into its two optically active components.

Stereoisomeric *diphenylethylene oxides* have been prepared from hydrobenzoin by Read.[6] The symmetrical compound I is inactive, but

[1] E. C. Dodds, L. Goldberg, W. Lawson and R. Robinson, *Proc. Roy. Soc.*, 1939, **B127**, 140. [2] A possible explanation of the specific action of the cyanide in effecting this condensation has been suggested by A. Lapworth, *J. C. S.*, 1903, **83**, 995. [3] J. S. Buck and W. S. Ide, *J. A. C. S.* 1930, **52**, 220, 4107; 1931, **53**, 2350, 2784. [4] *J. C. S.*, 1908, **93**, 309; 1909, **95**, 583; 1913, **103**, 112. [5] E. Erlenmeyer, jun., *Ber.*, 1897, **30**, 1530. [6] J. Read and I. G. M. Campbell, *J. C. S.*, 1930, 2377.

the dissymmetric oxide II exists in a racemic form and in two optical isomers of high activity.

I.  II. 

If benzoin is reduced with zinc and alcoholic hydrochloric or acetic acid, instead of with sodium amalgam, the alcoholic group alone is attacked and desoxybenzoin formed.

$$C_6H_5.\overset{O}{\overset{\|}{C}}—\overset{OH}{CH}.C_6H_5+2H = C_6H_5.\overset{O}{\overset{\|}{C}}—CH_2.C_6H_5+H_2O$$

Desoxybenzoin.

Desoxybenzoin, *benzyl-phenyl-ketone*, is generally prepared by the above method. It is also formed by the usual methods for preparing ketones, *e.g.* by distilling a mixture of calcium benzoate and calcium phenyl-acetate, or from phenyl-acetyl chloride, $C_6H_5.CH_2.COCl$, and benzene in the presence of aluminium chloride. It crystallises in colourless plates, m.p. 60° and b.p. 314°, and on energetic reduction yields dibenzyl. Desoxybenzoin resembles aceto-acetic ester in that one hydrogen atom of the methylene group is replaceable by sodium and alkyl groups.

$$C_6H_5.CO.CHNa.C_6H_5+ICH_3 = C_6H_5.CO.\overset{CH_3}{\overset{|}{C}}H.C_6H_5+NaI$$

Methyl-desoxybenzene.

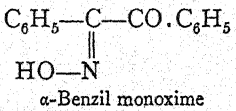
The presence of a secondary alcoholic grouping in benzoin is also shown by the behaviour of the compound on oxidation with nitric acid, when CHOH is converted into CO with the production of dibenzoyl or benzil :

$$C_6H_5.CO.CHOH.C_6H_5+O = C_6H_5.CO.CO.C_6H_5+H_2O$$

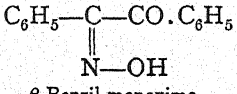
Benzil.

Benzil, *dibenzoyl*, *diphenyl-glyoxal*, forms yellow prisms, m.p. 95°. Owing to the ease with which it is prepared, it is one of the most accessible of the α-diketones. Among its derivatives the oximes are of special interest, since the study of these compounds has contributed largely to our knowledge of the stereochemistry of the nitrogen atom.[1]

Two monoximes and three dioximes of benzil are known. An examination of the chemical behaviour of the monoximes has led to them being assigned the following space formulæ [2] :



α-Benzil monoxime
m.p. 140°

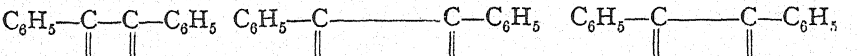


β-Benzil monoxime
m.p. 113°.

[1] V. Meyer and Auwers, *Ber.*, 1888, **21**, 790, 815. Hantzsch and Werner, *Ber.*, 1890, **23**, 11. Beckmann and Köster, *Ann.*, 1893, **274**, 15. [2] These are the newer arrangements as proposed by Meisenheimer. For preparation see T. W. J. Taylor and M. S. Marks, *J. C. S.*, **1930**, 2302.

For methods of determining the configuration of the stereoisomeric ketoximes, see p. 57.

The configurations of the three isomeric benzil-dioximes are now written as follows, involving a transposition of the formulæ previously ascribed to the α- and β-forms [1]:

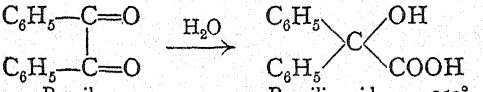


α- or *anti*-form m.p. 243-244°

β- or *syn*-form m.p. 206°

γ- or *amphi*-form m.p. 164-165°.

A peculiar property of benzil is the change it undergoes when heated with alcoholic potash, when an intramolecular rearrangement takes place with the formation of *benzilic acid*:



Benzil

Benzilic acid, m.p. 150° (Diphenyl-glycollic acid).

This reaction resembles the conversion of phenanthraquinone into diphenylene-glycollic acid (p. 505), and of β-naphthaquinones into oxindene-carboxylic acids.

s-**Tetraphenyl-ethane**, $(C_6H_5)_2CH.CH(C_6H_5)_2$, is obtained in various ways, *e.g.* by the interaction of chloral and benzene in the presence of aluminium chloride. It forms colourless crystals, m.p. 207·5° and b.p. 379° to 383°.

Unsymmetrical tetraphenyl-ethane, $(C_6H_5)_3C.CH_2.C_6H_5$, has been prepared by the action of benzyl-magnesium chloride on triphenyl-chloromethane.[2]

$$(C_6H_5)_3C.Cl+C_6H_5.CH_2.MgCl = (C_6H_5)_3C.CH_2.C_6H_5+MgCl_2$$

It crystallises in monoclinic crystals, m.p. 144°.

Tetraphenyl ethylene, $(C_6H_5)_2C:C(C_6H_5)_2$, m.p. 221°, can be obtained by the action of zinc dust on benzophenone chloride.

Pentaphenyl ethane, $(C_6H_5)_3C.CH(C_6H_5)_2$, results when a mixture of diphenyl-bromo-methane and triphenyl-chloro-methane, in ethereal solution, is treated with magnesium.[2] It melts about 175° to 180°.

$$(C_6H_5)_3C.Cl+Mg+Br.HC(C_6H_5)_2 = (C_6H_5)_3C.CH(C_6H_5)_2+MgClBr$$

Hydrocarbons containing phenyl groups linked to unsaturated carbon have the property of uniting directly with alkali metals,[3] as in the following examples (C$_6$H$_5$=Ph).

$$Ph_2C:CPh_2 \xrightarrow{2Na} Ph_2C(Na).C(Na)Ph_2$$

$$2Ph_2C:CH_2 \xrightarrow{2Na} Ph_2C(Na).CH_2.CH_2.C(Na)Ph_2$$

A similar addition is observed with certain hydrocarbons in which unsaturated carbon is linked to other unsaturated groups.

[1] J. Meisenheimer, *Ann.*, 1929, **469**, 130. In accordance with a proposal of Hantzsch the terms *syn-*, *anti-* and *amphi-* are employed in the sense indicated in the above formulæ in describing the stereoisomeric dioximes. (See also general notes in the chapter on "Stereochemistry.") [2] Gomberg and Cone, *Ber.*, 1906, **39**, 1461. [3] W. Schlenk and E. Bergmann, *Ann.*, 1928, **463**, 1, 98.

VI.—HIGHER HOMOLOGUES OF DIPHENYL-ETHANE AND THEIR DERIVATIVES

Whereas the compounds already described in this chapter contain aromatic residues linked together by one or two "methane" carbon atoms, a number of substances are also known in which a longer aliphatic chain is present between the aromatic groups.

Dibenzyl-methane, *αγ-diphenyl-propane,* $C_6H_5.(CH_2)_3.C_6H_5$, b.p. 299°, is formed by reducing dibenzyl-ketone, $C_6H_5.CH_2.CO.CH_2.C_6H_5$ (m.p. 40°, b.p. 330°), by means of hydriodic acid. The ketone is obtained by the dry distillation of calcium phenyl-acetate.[1] We may also consider as derivatives of dibenzyl-methane certain of the polyketones discussed in previous chapters, which are of interest in connection with the theory of tautomerism. Among these are *dibenzoyl-methane,* $(C_6H_5CO)_2CH_2$, *dibenzoyl-acetyl-methane,* $(C_6H_5CO)_2CH(COCH_3)$, and *tribenzoyl-methane,* $(C_6H_5CO)_3CH$.

αγ-Tetraphenyl-propane, $(C_6H_5)_2CH.CH_2.CH(C_6H_5)_2$, m.p. 139°, is formed by the reduction of tetraphenyl-allene with phosphorus and hydrogen iodide, or with sodium and alcohol. **Tetraphenyl-allene** [2] is produced when the barium salt of diphenyl-acetic acid is distilled, tetraphenyl-acetone being obtained as an intermediate product:

$$(C_6H_5)_2CH.CO.O.Ba.O.OC.CH(C_6H_5)_2 \xrightarrow{-BaCO_3}$$

$$(C_6H_5)_2CH.CO.CH.(C_6H_5)_2 \xrightarrow{-H_2O} (C_6H_5)_2C{:}C{:}C(C_6H_5)_2$$

Tetraphenyl-acetone — Tetraphenyl-allene.

A more convenient method of preparation is from benzal-acetophenone.[2] It forms colourless crystals of melting-point 164° to 165°.

Dibenzyl-ethane, *αδ-diphenyl-butane,* $C_6H_5.CH_2.CH_2.CH_2.CH_2.C_6H_5$, m.p. 52°, has been obtained by the reduction of diphenyl-butylene, $C_6H_5.CH{:}CH.CH_2.CH_2.C_6H_5$.

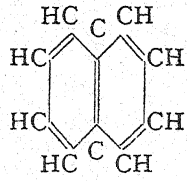
Diphenyl-diacetylene, $C_6H_5.C{\equiv}C{-}C{\equiv}C.C_6H_5$, a hydrocarbon closely related to indigo blue, is obtained by the oxidation of cuprous phenyl-acetylide, $C_6H_5.C{:}CCu$. As will be seen later, its ortho-dinitro-derivative may be converted into indigo.

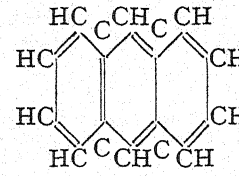
XIV

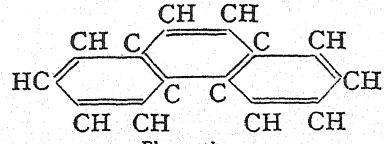
Condensed Polynuclear Compounds

Under this heading are described compounds containing several benzene nuclei linked together in such a manner that each pair possesses two carbon atoms in common, as in the following formulæ.

[1] H. Apitzsch, *Ber.*, 1904, **37**, 1428. [2] Vorländer and Siebert, *Ber.*, 1906, **39**, 1024.


Naphthalene


Anthracene.


Phenanthrene.

These hydrocarbons, like benzene, are found in coal tar, and as might be expected are on the whole aromatic in character.

An example of a compound formed by the combination of benzene nuclei with a five-membered carbon ring has previously been met with in *fluorene*. Owing to its genetic relationship to diphenyl-methane, however, this substance is more conveniently treated in the foregoing chapter. Another compound consisting of a benzene nucleus condensed with a five-membered ring is *indene*. This is treated in connection with naphthalene.

Naphthalene Group

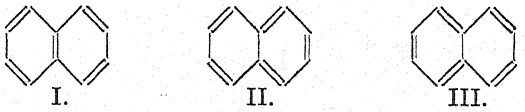
Naphthalene, $C_{10}H_8$, is obtained from the fraction of coal tar known as "middle or carbolic oil," boiling between 170° and 240° (see p. 378). The crystals which deposit from the oil on cooling are separated under pressure from liquid impurities, and further purified by heating with a small amount of sulphuric acid and subsequent sublimation. Naphthalene forms shining white rhombic leaflets of an unpleasant, penetrating smell and burning taste. It melts at 79°, boils at 218° and very readily sublimes. It is insoluble in water, dissolves with difficulty in cold alcohol, but readily in hot alcohol or in ether. With picric acid it forms a double compound, $C_{10}H_8$, $C_6H_2(NO_2)_3OH$, m.p. 149°, by means of which it can be quantitatively estimated.[1] The occurrence of naphthalene in coal tar is probably due to the ease with which it is formed when organic substances are heated to a high temperature in absence of air. It is a compound of great industrial value, serving as it does for the preparation of naphthols, naphthylamines, etc., for dye-stuffs, and also of the phthalic acid required in the synthesis of indigo. Its use as a preventative against moths is well known.

Constitution and Synthesis of Naphthalene

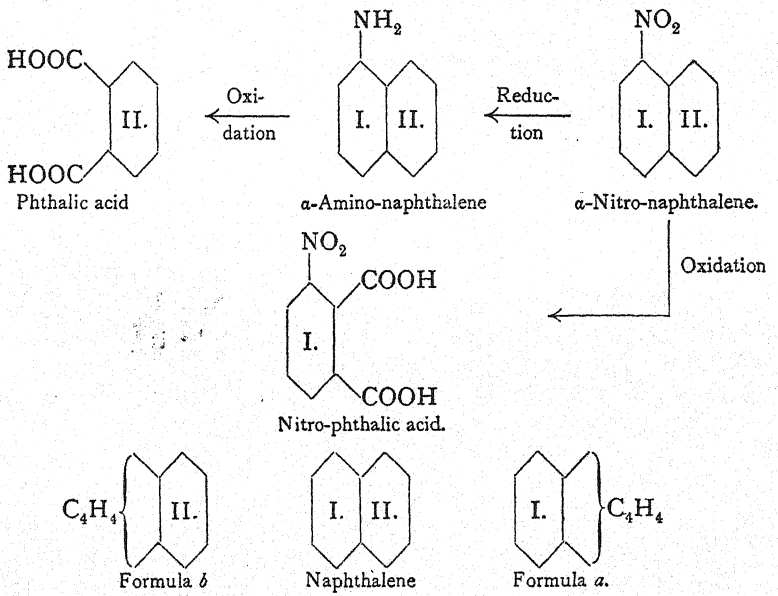
The symmetrical formula for naphthalene given above, according to which two benzene rings are joined together with two carbon atoms

[1] W. P. Jorissen and J. Rutten, *Chem. Weekblad.*, 1909, 6, 261.

in common,[1] was first put forward by Erlenmeyer in 1866. Although insufficient to meet all the facts of the case, this formula satisfactorily explains the isomerism observed among naphthalene derivatives, and if modified in accordance with the modern conception of resonance it also gives a good representation of the chemical behaviour of naphthalene. It will be remembered that a somewhat similar difficulty exists in connection with the Kekulé formula for benzene. The molecule of naphthalene is now regarded as existing in a state of resonance (see p. 88). The three principal contributing forms are the following, of which the symmetrical arrangement I is somewhat more important than the other two.



Proof of the presence of two benzene rings, having two adjacent carbon atoms in common, is furnished by the *behaviour of naphthalene and its substitution products on oxidation.*[2] When naphthalene itself is oxidised it yields phthalic acid (see p. 452). Consequently the formula $C_{10}H_8$ of naphthalene may, as a first step, be expanded to $C_6H_4{=}C_4H_4$. Now α-nitro-naphthalene, which is obtained from naphthalene on treatment with nitric acid and which may be supposed [3] to have the nitro-group attached to benzene ring I (below), yields on oxidation nitro-phthalic acid. Hence in this case the benzene nucleus I remains intact and the



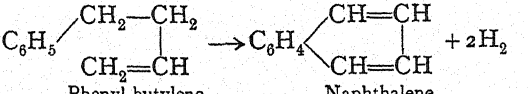
[1] Unsymmetrical formulæ for naphthalene have lately been advocated by Auwers and Frühling (*Ann.*, 1921, **422**, 211) and by Mayer and Bansa (*Ber.*, 1921, **54**, 19). *Cf.* also Weinberg, *Ber.*, 1921, **54**, 2168. [2] Graebe, *Ann.*, 1866, **149**, 20. [3] It will readily be seen that the argument is not affected by this assumption. The nitro-group could equally well be supposed to be contained in the nucleus II.

group C_4H_4 is again oxidised away to two carboxyl groups, leading to formula *a* for naphthalene. If, however, nitro-naphthalene is reduced to the amino-compound and subsequently oxidised, phthalic acid and not amino-phthalic acid is obtained. Here ring I has been destroyed and II remains unchanged, thus giving formula *b* for naphthalene.

On comparing the formulæ *a* and *b*, it is seen at once that the group C_4H_4 must be united to two adjacent carbon atoms of the ring I or II to form a new benzene ring, *i.e.*, that naphthalene must consist of two symmetrically joined benzene nuclei.

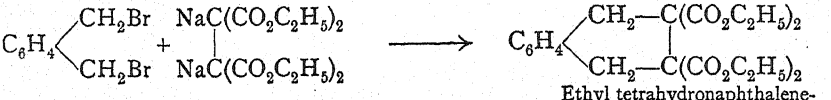
This structure is also confirmed by a number of *syntheses of naphthalene and its derivatives*, among which the following may be mentioned.

1. Naphthalene is formed when phenyl-butylene or its dibromide is led in the vaporous state over red-hot lime.



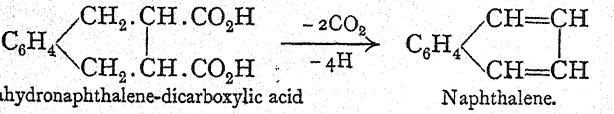
Phenyl-butylene Naphthalene.

2. Baeyer and Perkin prepared naphthalene and derivatives of tetrahydro-naphthalene by bringing *o*-xylylene dibromide into reaction with the disodium compound of ethane tetracarboxylic ester.



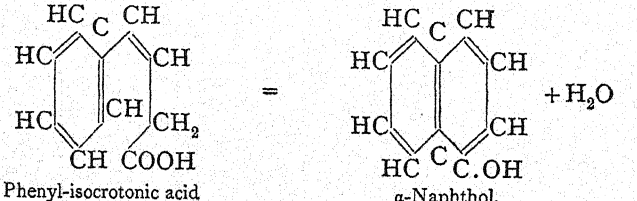
Ethyl tetrahydronaphthalene-tetracarboxylate.

When the ester so obtained is boiled with alkali it is hydrolysed with the simultaneous removal of carbon dioxide, to give tetrahydro-naphthalene dicarboxylic acid, from which, by distillation of the silver salt, naphthalene itself was prepared.



Tetrahydronaphthalene-dicarboxylic acid Naphthalene.

3. Phenyl-isocrotonic acid, on being heated, is converted into α-naphthol, a monohydroxy derivative of naphthalene [1]:

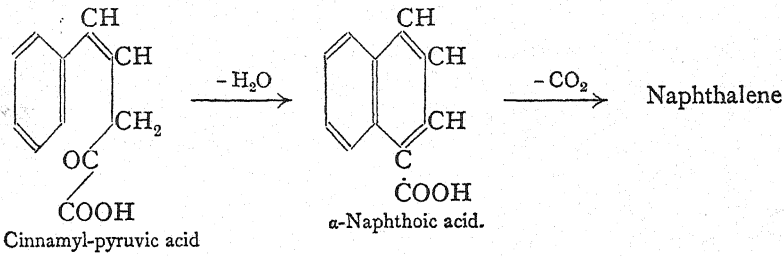


Phenyl-isocrotonic acid α-Naphthol.

4. When cinnamylidene-hippuric acid, or the cinnamyl-pyruvic acid obtained from it on decomposition, is heated with concentrated hydro-

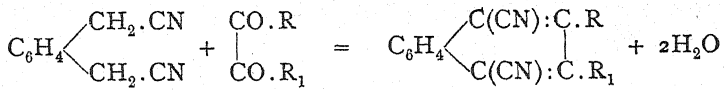
[1] Fittig and Erdmann, *Ber.*, 1883, **16**, 43. *Ann.*, **275**, 284.

chloric acid at 110° to 120°, α-naphthoic acid, and finally naphthalene, is produced.[1]



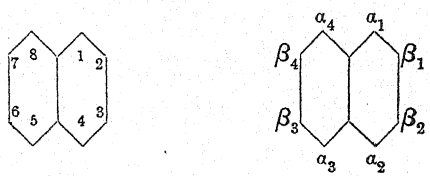
Cinnamyl-pyruvic acid α-Naphthoic acid.

5. *o*-Xylylene cyanide condenses with compounds such as *o*-diketones, ketonic esters and oxalic esters, in the presence of sodium ethoxide, to yield naphthalene derivatives.[2]



Isomerism of Naphthalene Derivatives

From the formula for naphthalene it is possible to predict the existence of a number of isomeric substitution products. In order to indicate the position of substituent atoms or radicals, use is made of one or other of the following systems :



It will be seen that even the mono-derivatives of naphthalene can exist in two series, according to whether or not the substituent is attached to an atom adjacent to one of the two carbon atoms common to both rings. Those compounds formed by the replacement of one of the four equivalent hydrogen atoms 1, 4, 5, or 8 are known as α-compounds, and those obtained by substituting one of the four equivalent atoms 2, 3, 6, or 7 as β-compounds. Whether a radical is attached in the α- or β-position can frequently be determined by oxidising the substance under consideration to the corresponding phthalic acid derivative (*cf.* p. 529).

A disubstitution product of naphthalene may occur in 10 isomerides if the two substituents are similar, or in 14 isomerides if they are different. With the entry of more than two atoms or groups into the molecule the number of isomerides is very much larger.

Compounds in which two substituents are attached to two adjacent carbon atoms correspond in their behaviour to the ortho-derivatives of the benzene series. Similar behaviour with respect to anhydride formation

[1] E. Erlenmeyer and Kunlin, *Ber.*, 1902, 35, 384. [2] O. Hinsberg, *Ber.*, 1910, 43, 1360.

and condensation is also shown by 1 : 8- or 4 : 5-derivatives, these positions being known as *peri*-positions. **Peri-derivatives** possess in an enhanced degree the properties characteristic of *o*-compounds. This may be seen from a comparison of *peri*-amino-naphthoic acid with anthranilic acid, of naphthalic with phthalic acid, and of 1 : 8-naphthylene-diamine with *o*-phenylene-diamine. In all cases where *o*-diamines are able to take up a new element to form a five-membered ring-system, the *peri*-diamines can similarly form a six-membered ring. In the latter case, however, the reaction occurs much more readily than with the *o*-derivatives.[1]

Chemical Behaviour of Naphthalene

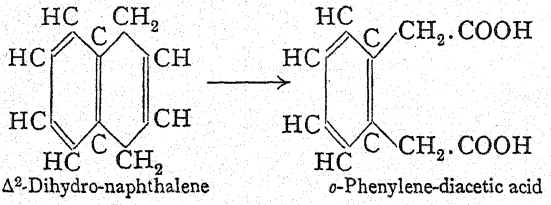
As already stated, naphthalene shows in general the properties characteristic of aromatic hydrocarbons. It reacts with halogens, nitric acid and sulphuric acid in a similar manner to benzene, with the formation of chloro-, nitro- and sulphonic derivatives. In many ways, however, it differs from benzene.

The chief distinction between benzene and naphthalene is the ease with which the latter forms additive compounds, the addition beginning at the α-positions.

In this respect naphthalene is less saturated than benzene. On reduction, for example, it first yields $\alpha_1\alpha_2$-dihydro-naphthalene, and on oxidation it readily gives α-naphthaquinone (see index). Halogen is very easily added on, and as in the case of direct substitution, again leads to the exclusive formation of α-derivatives. Exceptional behaviour is shown on sulphonation, which yields a mixture of α- and β-sulphonic acids.

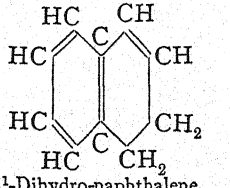
$\alpha_1\alpha_2$-Dihydro-naphthalene, Δ^2-dihydro-naphthalene, $C_{10}H_{10}$, is obtained when naphthalene is reduced with sodium in boiling alcoholic solution. It melts at 15° and boils at 212°. On oxidation the compound is converted into *o*-phenylene-diacetic acid, proving that the hydrogen atoms have assumed the 1 : 4-position.

I.



Δ^2-Dihydro-naphthalene — *o*-Phenylene-diacetic acid

II.



Δ^1-Dihydro-naphthalene.

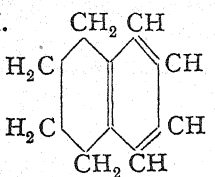
Dihydro-naphthalene resembles ethylene in its unsaturated properties, two monovalent atoms or groups (H_2, Br_2, HOCl, etc.) being readily added on to the β_1 β_2 positions. On the other hand, dihydro- and tetrahydro-naphthalene both possess the tendency characteristic of partially hydrogenated aromatic systems to pass into true aromatic types, as shown by their decomposition merely on heating to give naphthalene and hydrogen. If symmetrical Δ^2-dihydro-naphthalene is heated to 140°

[1] Bamberger, *Ber.*, 1887, **20**, 241. Sachs, *Ann.*, 1909, **365**, 53.

with 5 per cent. sodium ethylate solution,[1] the position of the double bond is shifted with the formation of **Δ^1-dihydro-naphthalene** (II), m.p. $-7°$. The constitution of this compound is shown by the production of hydrocinnamic-*o*-carboxylic acid on oxidation with permanganate, in the same manner as Δ^2-dihydro-naphthalene gives *o*-phenylene-diacetic acid.

1:2:3:4-Tetrahydro-naphthalene, tetralin (III), has recently become readily accessible[2] and is prepared industrially on a large scale. In the technical preparation, naphthalene is first fused with finely-divided metals of low melting-point in order to remove sulphur and other compounds, which would "poison" the catalyst used in subsequent operations. The purified naphthalene is then placed in an autoclave provided with stirring apparatus and treated with hydrogen under pressure, in the presence of a nickel salt. The reaction slows down after four atoms of hydrogen have been taken up. As the change is an exothermic one, heat need only be supplied to start the reaction.

III.



Tetrahydro-naphthalene, tetralin.

The tetralin of commerce is a colourless liquid, b.p. 206° to 208°, D^{20} 0·974 to 0·976, m.p. $-30°$ to $-27°$, and flash-point 78°. At the ordinary temperature the substance is stable, but the hot vapour is oxidised in air. Tetralin is a good solvent for sulphur, fats, resins and many other organic products, and hence is employed industrially as a solvent in the preparation of varnishes and lacquers, and admixed with benzene and alcohol as a fuel for internal combustion engines. Pure tetralin is obtained from the sulphonic acid by the action of superheated steam (b.p. 206·5° at 755 corr.).

When tetralin is treated with bromine[3] it behaves in the same manner as an alkyl benzene. In the cold, no reaction takes place in the absence of light; but on the addition of a little iron or a trace of iodine, substitution readily occurs in the benzene nucleus, even at $-10°$, with the formation of a mixture of *ar*-α- and *ar*-β-bromo-tetrahydro-naphthalenes,[4] b.p. 140° to 145° under 15 mm. Under the influence of light, or at a higher temperature in the absence of catalysts, halogen attacks the reduced ring.

Substitution in the aromatic half of tetralin does not follow the same laws as in the case of naphthalene.[5] Reactions such as nitration, bromination and chlorination yield a mixture of *ar*-α- and *ar*-β-substitution products, which can often be satisfactorily separated by distillation and freezing out; whereas naphthalene gives almost exclusively α-compounds, and the corresponding β-derivatives can only be obtained by more or less troublesome indirect methods. Other reactions, such as the entrance of carboxyl, alkyl and acyl groups into tetralin under the influence of

[1] F. Straus and Lemmel, *Ber.*, 1913, **46**, 232. For dihydro-naphthalene, see also Willstätter and King, *Ber.*, 1913, **46**, 527. [2] G. Schroeter, *Ann.*, 1922, **426**, 1, 17, 83. *Ber.*, 1924, **57**, 1990. [3] J. v. Braun and Kirschbaum, *Ber.*, 1921, **54**, 597. [4] The prefix *ar*- refers to the unreduced or aromatic half of the molecule. [5] J. v. Braun, Hahn and Seemann, *Ber.*, 1922, **55**, 1687.

aluminium chloride, proceed almost completely in the direction of the β-compounds, whilst with naphthalene, on the other hand, the same conditions frequently furnish a difficultly separable mixture of α and β-products. Since tetralin and its substitution products readily give up hydrogen to form the corresponding naphthalene compounds, we have here an indirect method of preparing from tetralin those derivatives of naphthalene which can only be obtained with much labour by direct means.

Decahydro-naphthalene, decalin, $C_{10}H_{18}$, is prepared from tetralin by further hydrogenation with fresh catalyst under 12 to 15 atmospheres pressure. It boils at 189° to 191°. D_4^{18} 0·8842. Hückel [1] has shown that decalin exists in a *cis*-form (b.p. 193°, D_4^{20} 0·898, n_D^{20} 1·48279) and a *trans*-modification (b.p. 185°, D_4^{20} 0·872, n_D^{20} 1·47009).

Naphthalene dichloride, $C_{10}H_8Cl_2$, is produced as a yellow oil when naphthalene is treated with potassium chlorate and hydrochloric acid. At about 50° it begins to decompose into hydrochloric acid and α-chloro-naphthalene. **Naphthalene tetrachloride,** $C_{10}H_8Cl_4$, m.p. 182°, is formed by leading chlorine into a solution of naphthalene in chloroform. On boiling with alcoholic potash it is converted into dichloro-naphthalene. As would be expected, all four chlorine atoms are contained in the same benzene ring, since when oxidised with nitric acid the compound yields phthalic acid.

With ozone naphthalene forms an explosive crystalline **diozonide** in which two molecules of ozone are attached to one of the benzene nuclei.

SUBSTITUTION PRODUCTS OF NAPHTHALENE [2]

(a) Homologues

α-Methyl-naphthalene, $C_{10}H_7.CH_3$, m.p. −20°, b.p. 240° to 243°, and *β-methyl-naphthalene*, m.p. 32·5°, b.p. 241° to 242°, are found with dimethyl-naphthalenes in coal tar, petroleum and guaiacum resin.[3] Synthetically they may be prepared by methods similar to those employed for the benzene homologues, such as by treating the bromo-naphthalenes with alkyl halides and sodium, and by the Friedel-Crafts reaction from alkyl iodides or bromides and naphthalene in the presence of aluminium chloride.

(b) Halogen and Nitro-derivatives

As already mentioned, the action of chlorine or bromine on the hydrocarbon yields α-substitution products. The β-halogen compounds are best prepared from the hydroxy-, amino- or sulphonic derivatives by replacing the substituent with halogen according to methods described under benzene. The halogen atoms in these derivatives are less difficult to remove than those in the corresponding benzene compounds, but are nevertheless far more firmly attached than in the alkyl halides, and cannot be exchanged by boiling with aqueous alkalis.

α-Chloro-naphthalene, $C_{10}H_7Cl$, boils at 263°. It is formed by the chlorination of boiling naphthalene, but is best prepared from α-amino-naphthalene by way of the

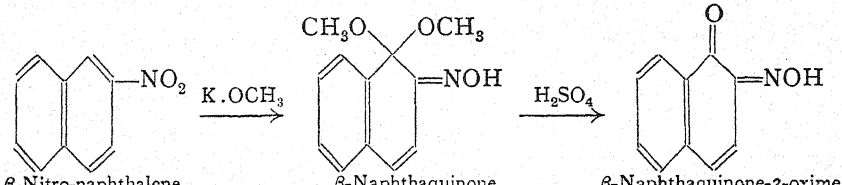
[1] *C.*, 1923, **III**, 766. R. Willstätter and F. Seitz, *Ber.*, 1924, **57**, 683. [2] For a useful summary of naphthalene derivatives see *Naphthalin Derivate*, by van der Kam (M. Nijhoff, Hague, 1927). [3] See *Ber.*, 1918, **51**, 1603. *Ber.*, 1919, **52**, 346, 370.

diazo-compound. **β-Chloro-naphthalene** melts at 61° and boils at 265°. **Dichloro-naphthalene,** $C_{10}H_6Cl_2$, is known in all of the ten possible isomeric forms.

The nitration of naphthalene with concentrated nitric acid at ordinary temperature leads mainly to the formation of **α-nitro-naphthalene,** free from the isomeric β-compound. It crystallises in yellow needles; m.p. 61°, b.p. 304°. By way of the amino- and diazo-derivatives it may be converted into the hydroxy compound, α-naphthol, identical with the product obtained synthetically from phenyl-isocrotonic acid (see p. 530). Hence the nitro-group must have occupied the α-position. Since the nitro-group can be exchanged by the usual methods for a variety of atoms and radicals, α-nitro-naphthalene has frequently been of aid in determining the position of the substituent in mono-derivatives of naphthalene. It is used industrially in the preparation of α-naphthylamine.

Energetic nitration of naphthalene at higher temperature yields di-, tri- and tetra-nitro-naphthalenes, of which the first are of importance in the dye-stuff industry.

β-Nitro-naphthalene is prepared from technical β-naphthylamine by diazotisation in nitric acid solution and treating the naphthalene diazonium nitrate with cuprous oxide [1]; or from β-nitro-tetralin by dehydrogenation with the aid of bromine.[2] It forms yellow crystals, m.p. 79°. Under the influence of methyl alcoholic potash it undergoes a peculiar reaction,[3] similar to that given by 9-nitro-anthracene, and becomes transformed into an alkali-soluble compound which on further treatment with mineral acid yields naphthaquinone-oxime, isomeric with the original nitro-naphthalene.[4]



β-Nitro-naphthalene — β-Naphthaquinone 2-oxime-dimethylacetal — β-Naphthaquinone-2-oxime (2-nitroso-1-naphthol).

(c) Naphthalene Sulphonic Acids, Naphthols, Naphthylamines

When heated with concentrated sulphuric acid, naphthalene gives a mixture of the two isomeric **naphthalene-sulphonic acids,** $C_{10}H_7.SO_2OH$; below 100° more of the α-form is produced and above 160° more of the β-compound. These reactions are reversible, in the sense $C_{10}H_7.SO_3H + H_2O \rightleftharpoons C_{10}H_8 + H_2SO_4$. The α-acid, however, is hydrolysed to naphthalene many times more rapidly than the β-compound, and this difference between the two forms becomes more pronounced

[1] For laboratory details see Meisenheimer and Witte, *Ber.*, 1903, **36**, 4153. [2] J. v. Braun and co-workers, *Ber.*, 1922, **55**, 1695. [3] Meisenheimer and Witte, *loc. cit.*, p. 4164. [4] Another change occurs simultaneously, though to a much smaller extent, leading to the formation of azoxy- and azo-compounds by the reducing action of the methyl alcoholic potash on β-nitro-naphthalene (*cf.* nitrobenzene).

with rise in temperature and with increasing concentration of sulphuric acid.[1] Consequently, higher temperatures and stronger sulphuric acid favour the production of naphthalene β-sulphonic acid.

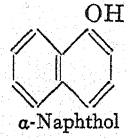
Under selected conditions of acid concentration and temperature it is possible to convert naphthalene-α-sulphonic acid into naphthalene without causing β-sulphonation. This mobility of the α-group is also observed in the reaction of the sodium α- and β-sulphonates towards fused caustic alkali (see below), and an α-sulphonic group may be replaced by hydroxyl under conditions which leave the β-sulphonic group untouched. This property is of great value in the preparation of dyestuff intermediates, *e.g.* H-acid.

The α- and β-sulphonic acids are deliquescent crystalline solids, the sodium salts of which on being fused with caustic alkali yield the corresponding naphthols :

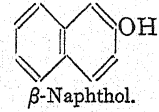
$$C_{10}H_7.SO_3Na + 2NaOH = C_{10}H_7.ONa + Na_2SO_3$$

On the large scale one part of sodium naphthalene-sulphonate is melted under pressure at about 300° with a concentrated solution of two parts of sodium hydroxide, in iron vessels provided with stirring apparatus. From the sodium naphtholate so formed, naphthol may be precipitated by means of sulphuric acid or carbon dioxide, and purified by distillation alone or with superheated steam.

α-Naphthol, m.p. 94° and b.p. 280°, crystallises in needles. Owing to the difficulty of preparing sodium naphthalene-α-sulphonate free from the β-compound, α-naphthol is best obtained from α-naphthylamine by hydrolysis with 10 per cent. sulphuric acid at 200°. For a synthesis see p. 530. **β-Naphthol,** m.p. 122° and b.p. 286°, forms leaflets ; it is pre-



α-Naphthol



β-Naphthol.

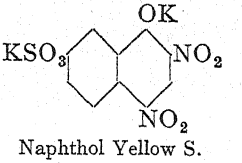
pared by alkali fusion of sodium naphthalene-β-sulphonate. In chemical behaviour the naphthols show a general resemblance to the phenols, although the hydroxyl groups are much more mobile than in the latter compounds. For example, when heated with ammonia the naphthols are readily converted into the naphthylamines. On reduction with sodium and alcohol, naphthols yield *tetrahydro-naphthols*, $C_{10}H_{11}.OH$. In the case of α-naphthol the four hydrogen atoms almost exclusively enter the hydroxyl-free ring to form ***ar*-tetrahydro-α-naphthol,**[2] $(C_4H_8) : C_6H_3.OH$, which possesses the character of a true phenol. With β-naphthol the four hydrogen atoms not only enter the hydroxyl-free ring to give ***ar*-tetrahydro-β-naphthol,** $(C_4H_8) : C_6H_3OH$, but also that containing the —OH group to form ***ac*-tetrahydro-β-naphthol,** $(HO.C_4H_7) : C_6H_4$. The first of these resembles the phenols in properties, and the latter the aliphatic alcohols. These interesting differences are discussed in more detail under the naphthylamines.

[1] R. Lautz, *Bull. Soc. Chim.*, 1935, [v], 2, 2092. [2] For the use of the prefixes *ar-* and *ac-* see p. 533.

A large number of ethers, sulphonic acids and nitro-derivatives of the naphthols have been prepared. The hydroxy-derivatives of the naphthalene series also resemble the phenols in reacting in tautomeric forms.

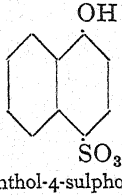
β-Naphthyl methyl ether, $C_{10}H_7.OCH_3$, m.p. 72°, is obtained by heating β-naphthol with methyl alcohol and hydrochloric acid, or by heating sodium β-naphtholate with potassium methyl sulphate. It has a smell like oil of orange flowers (neroli oil), and is used under the name of **nerolin** in the preparation of perfumes.

Dinitro-α-naphthol, $C_{10}H_5(NO_2)_2OH$, $[\overset{1}{O}H.\overset{2}{N}O_2.\overset{4}{N}O_2]$, is prepared by treating α-naphthol-disulphonic acid (1 : 2 : 4) with nitric acid, and crystallises in needles, m.p. 138°. It is almost insoluble in water but its salts are comparatively soluble, the sodium or less frequently the potassium compound being placed on the market under the name of **Martius yellow.** In acid bath it dyes wool and silk a golden yellow colour. **Naphthol yellow S** is the potassium salt of the sulphonic derivative of dinitro-α-naphthol. It is a more permanent dye than Martius yellow.

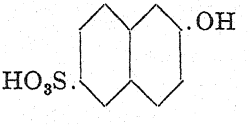


Naphthol Yellow S.

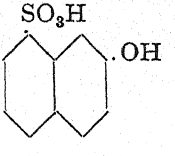
Naphthol-sulphonic acids are produced either by direct sulphonation, by fusing polysulphonic derivatives of naphthalene with alkali hydroxide, or by replacing the NH_2-group in naphthylamine sulphonic acids with the hydroxyl group. They are extensively used in the dyeing industry. Among the more important are the following :



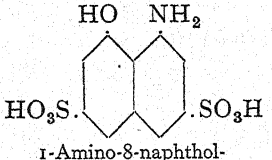
1-Naphthol-4-sulphonic acid (Nevile and Winther's acid)



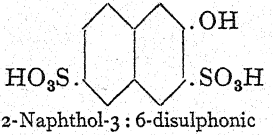
2-Naphthol-6-sulphonic acid (Schäffer's or β-acid)



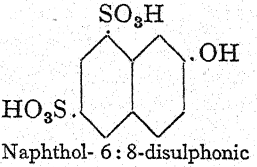
2-Naphthol-8-sulphonic acid (Croceic acid, α-acid).



1-Amino-8-naphthol-3 : 6-disulphonic acid (H-acid)



2-Naphthol-3 : 6-disulphonic acid (R-acid)



2-Naphthol- 6 : 8-disulphonic acid (G-acid).

Among the numerous sulphonic acids of the naphthols those named above are the ones chiefly used in the preparation of azo-dyes. Nevile and Winther's acid and *disulphonic acids H, R and G* are of particular value. The two last are formed by the vigorous sulphonation of β-naphthol and can be separated by taking advantage of the different solubilities of their acid sodium salts in alcohol, that of the G-acid being readily soluble and that of the R-acid almost insoluble. Whereas 2-naphthol-8-sulphonic

acid and G-acid generally yield yellowish dyes when coupled with diazonium compounds, Schäffer's acid and R-acid give bluish dyes.

In addition to the azo-dyes described on p. 415, the following derived from naphthol-sulphonic acids and diazotised amines may also be mentioned :

Crocein orange, $C_6H_5.\overset{1}{N}:N.C_{10}H_5(\overset{2}{O}H)SO_3\overset{6}{H}$, from aniline and Schäffer's acid.

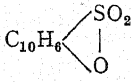
Ponceau, from aniline and R-acid.

Bordeaux B, from α-naphthylamine and R-acid.

Orange G, from aniline and G-acid.

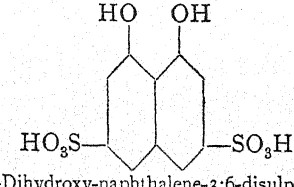
Finally, it should be noted that important dyes (such as **Roccellin,** $SO_3H.C_{10}H_6$—N : N—$C_{10}H_6OH$) are derived from *α-naphthalene-azo-β-naphthol,* $C_{10}H_7$—N : N—$C_{10}H_6OH$, which is obtained by coupling diazotised α-naphthylamine with β-naphthol.

Sulphonic acids of α-naphthol containing hydroxyl and sulphonic groups in the *peri*-positions (1 : 8) very readily split off water between the SO_3H and OH groups, with the formation of **sultones.** 1 : 8-Naphthol-sulphonic acid yields *naphtha-sultone,*



the simplest compound of this type.

A number of isomeric dihydroxy-naphthalenes are known, among which *peri*-**dihydroxy-naphthalene** may be specially noted, since in consequence of the adjacent position of the two hydroxyl groups it resembles *o*-dihydroxy compounds in forming mordant dyes. This property is utilised in azo-dyes prepared from a disulphonic acid of *peri*-dihydroxy-naphthalene, which are classed together under the name of **chromotrope** dyes. The acid itself is consequently termed **chromotropic acid.**



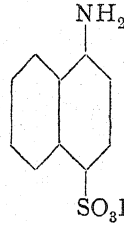
1:8-Dihydroxy-naphthalene-3:6-disulphonic acid, chromotropic acid.

The colours produced with azo-dyes derived from this acid undergo surprising variations with change of metallic mordant. For example, the dye prepared from diazotised aniline dyes wool in acid bath a red colour. Aluminium salts transform this colour to violet and chromates to blue-black.

α- and β-**Naphthylamines,** $C_{10}H_7.NH_2$, can be prepared by reducing the corresponding nitro-compounds, or from the naphthols by heating under pressure with ammonia. In the presence of ammonium sulphite (*Bücherer's* reaction) the latter reaction proceeds very readily. *α-Naphthylamine,* m.p. 50°, b.p. 300°, is usually obtained on the large scale by reducing α-nitronaphthalene with iron and hydrochloric acid. It possesses an unpleasant odour and is readily attacked by oxidising agents. Aqueous solutions of its salts give a blue precipitate with ferric chloride. *β-Naphthylamine,* m.p. 112°, b.p. 294°, is prepared technically by heating β-naphthol in iron autoclaves with ammonia and zinc chloride. It is

odourless and gives no coloration with oxidising agents. The naphthylamines and their sulphonic acids are largely employed in the manufacture of azo-dyes (see pp. 415 and 538).

On treatment with fuming sulphuric acid, α-naphthylamine yields **naphthionic acid** (formula see below), which corresponds to sulphanilic acid. When this compound is diazotised and coupled with β-naphthol, it is converted into **fast red A.** Naphthionic acid coupled with tetrazobenzidine chloride forms **Congo red** (see p. 416).



1:4-Aminonaphthalene-sulphonic acid, naphthionic acid.

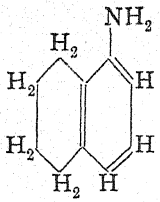
Among numerous amino-naphthol-sulphonic acids we may mention 1-*amino*-2-*naphthol*-6-*sulphonic acid*, the sodium salt of which is used as a photographic developer under the name of **eikonogen.**

Hydrogenated Naphthylamines [1]

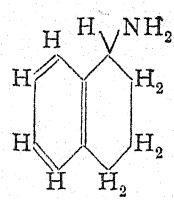
Each of the naphthylamines may be reduced to a tetrahydro-naphthylamine by the use of sodium and amyl alcohol, all four hydrogen atoms entering the same benzene nucleus. The compounds so obtained show striking differences in properties. If hydrogenation takes place in the ring containing the amino-group, as is mainly the case with β-naphthylamine, the product possesses the character of an aliphatic amine, or rather of a phenyl-substituted aliphatic amine. This type of reduction is distinguished as aliphatic-cyclic or *alicyclic hydrogenation*, and the compounds formed are written with the prefix *ac* (alicyclic). If, on the other hand, reduction occurs in the unsubstituted benzene nucleus, as is chiefly the case with α-naphthylamine, the product shows the properties of aniline and the aromatic bases. Hence reduction of this kind is termed *aromatic hydrogenation*, and the compounds are distinguished by the prefix *ar*. There are therefore four tetrahydro-naphthylamines known, the constitution of which may be expressed by the formulæ on p. 540.

That the hydrogen atoms always attach themselves asymmetrically, *i.e.*, to *one* of the two nuclei of the naphthalene molecule, was proved by Bamberger from an examination of the behaviour of the compounds with bromine and potassium permanganate. The above reduction products, for example, do not add on bromine at all, but if each nucleus had taken up two hydrogen atoms, then derivatives containing double bonds would have been formed which would have combined instantaneously with bromine.

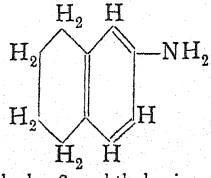
[1] E. Bamberger, *Ann.*, 1890, **257**, 1. J. v. Braun, *Ber.*, 1922, **55**, 3664.

I. 

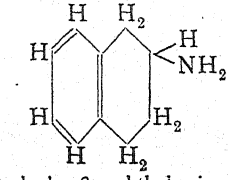
ar-Tetrahydro-α-naphthylamine

II. 

ac-Tetrahydro-α-naphthylamine.

III. 

ar-Tetrahydro-β-naphthylamine.

IV. 

ac-Tetrahydro-β-naphthylamine.

The *behaviour of the ac-hydrogenated bases* (II and IV) indicates, as already stated, that these have altogether lost the aromatic character of the parent substance and have gone over completely to the aliphatic type. They are strong bases, which turn turmeric paper brown and form salts of neutral reaction. They have a sharp smell resembling that of piperidine and exert a peculiar physiological action. On standing in air they rapidly absorb carbon dioxide. In contact with diazo-compounds they yield aliphatic diazo-amino-compounds of the general formula R—N_2—NHR. Their behaviour with nitrous acid is very characteristic; unlike the aromatic bases they form no diazonium salts but give crystalline and readily soluble nitrites. Hence they cannot be used for the preparation of dyes. When oxidised with potassium permanganate, the *ac*-tetrahydro-compounds, again unlike the *ar*-derivatives, are attacked in such a way that the reduced ring opens, and a benzene-dicarboxylic acid containing all the carbon of the original base is formed. Thus each of the *ac*-tetrahydro-naphthylamines yields on oxidation *o-carboxy-hydrocinnamic acid*, $C_6H_4\begin{cases}CH_2.CH_2.COOH\\COOH\end{cases}$.

In distinction to the above *ac*-bases, the *aromatic hydrogenated bases* (I and III) do not greatly differ from the parent substances containing four hydrogen atoms less, so that they may be considered as almost purely aromatic in type. *ar*-Tetrahydro-α-naphthylamine possesses the properties of a substituted aniline: it does not affect vegetable dyes, does not easily react with carbon disulphide, and is readily diazotised with nitrous acid. When it is oxidised with permanganate the ring containing the amino-group is entirely removed, with the formation of *adipic acid*, $COOH.CH_2.CH_2.CH_2.CH_2.COOH$.

It is worthy of emphasis that the influence of alicyclic as well as of aromatic hydrogenation is not confined to the reduced ring, but also makes itself felt in the adjacent ring. This is shown in the enhanced aromatic character of the latter, bringing it into still closer resemblance

to the ring of benzene derivatives. With reference to physical properties it may be noted that both the *ac*-and *ar*-hydrogenated bases have lower boiling-points than the parent amines, as will be seen from the following table.[1]

Parent Bases.	Hydrogenated Compounds.	
	Aromatic	Alicyclic.
α-Naphthylamine 300°	Tetrahydro 275°	Tetrahydro 246·5°
β-Naphthylamine 299·5°	,, 276·5°	,, 249·5°
α-Ethyl-naphthylamine 303°	,, 286-287°	,, —
β-Ethyl-naphthylamine 305°	,, 291·5°	,, 267°
α-Dimethyl-naphthylamine 274·5°	,, 261-262°	,, —
β-Dimethyl-naphthylamine 305°	,, 287°	,, —

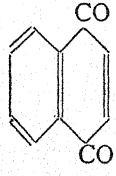
As already indicated on p. 540, the same regularities that have been observed in the case of the hydrogenated bases of naphthalene also hold true for the hydrogenated naphthols. The facts have been summed up by Bamberger as follows :—

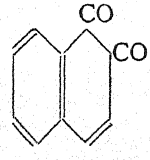
1. *When one of the two ring systems of naphthalene or its derivatives takes up four hydrogen atoms, this ring acquires the functions of an open aliphatic chain.*

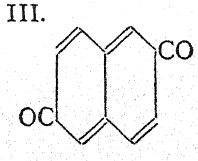
2. *Such hydrogenation results in the reduced compound behaving as a benzene derivative with an aliphatic side chain. The hydrogenated portion of the molecule exhibits aliphatic properties, and the non-hydrogenated portion aromatic properties.*

(d) Naphthaquinones and Naphthalene Carboxylic Acids

Three quinones of naphthalene are known, namely,

I. 
α- or 1:4-

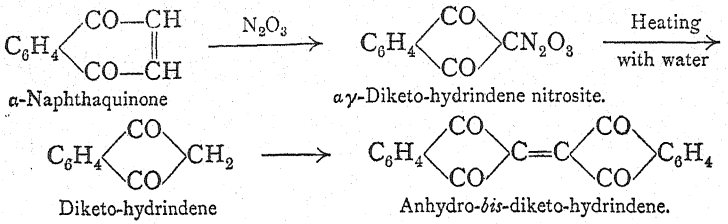
II. 
β- or 1:2-

III. 
amphi- or 2:6-naphthaquinone.

α-Naphthaquinone corresponds to *p*-benzoquinone. It is prepared by oxidising naphthalene with chromic acid in boiling glacial acetic acid. Better yields are obtained by oxidation of 1 : 4-dihydroxy-naphthalene, or of 1 : 4-aminonaphthol. It is also formed when naphthalene, dissolved in acetone containing sulphuric acid, is electrolytically oxidised at a platinum or lead anode. In its properties it strongly resembles quinone. It crystallises from alcohol in yellow needles, m.p. 125°, has a pungent smell and is very volatile. Sulphurous acid reduces it to 1 : 4-**dihydroxy-**

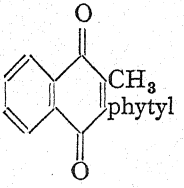
[1] Bamberger, *Ber.*, 1889, **22**, 773.

naphthalene, and with nitric acid it is oxidised to phthalic acid. Liquid nitrogen trioxide converts it into indene derivatives [1]:



The above is an example of the remarkable syntheses of indene derivatives, in which a six-membered carbon ring is transformed into a five-membered ring. This change also results from the action of chlorine or hypochlorous acid on naphthols, naphthaquinones and other naphthalene compounds.[2]

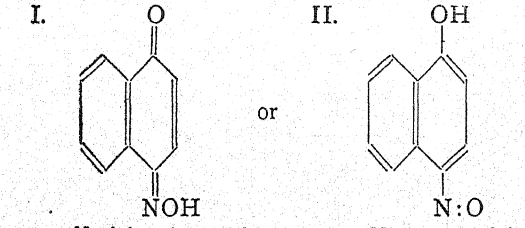
Many naturally occurring pigments are derived from α-naphthaquinone, *e.g.* juglone, plumbagin, lawsone and phthoicol, all of which are hydroxy or methylhydroxy derivatives. A development of great physiological importance is the synthesis of the anti-hæmorrhagic vitamin K_1, which is 3-phytyl-2-methyl-1:4-naphthaquinone.[3]



Carminic acid, the colouring matter of the cochineal insect (*Coccus cacti*), and **kermic acid,** the dye-stuff of *Coccus ilicis*, appear to be derivatives either of α-naphthaquinone or of anthracene.[4]

β-Naphthaquinone, which may be compared to *o*-benzoquinone, results from the oxidation of 1:2-amino-naphthol. It crystallises in red needles which decompose about 120°. It differs from the α-compound in being odourless and non-volatile. In chemical behaviour it resembles anthraquinone and even more closely phenanthraquinone. As will be seen later, the reactions of the latter are those of an ortho-diketone. Sulphurous acid reduces β-naphthaquinone to 1:2-dihydroxy-naphthalene.

When treated in alcoholic solution with hydroxylamine hydrochloride the naphthaquinones are converted into *naphthaquinone monoximes.*



These are identical with the compounds obtained by the action of nitrous

[1] J. Schmidt, *Ber.*, 1900, **33**, 543. [2] Zincke, *Ber.*, 1887, **20**, 2890, 3216; 1888, **21**, 2379, 2719; 1889, **22**, 1024, 2316. [3] L. F. Fieser, *J. A. C. S.*, 1939, **61**, 3467. This synthesis confirms the degradative work of Doisy, *ibid.*, **61**, 2558. [4] O. Dimroth, *Ber.*, 1910, **43**, 1387; *Ann.*, 1913, **399**, 1.

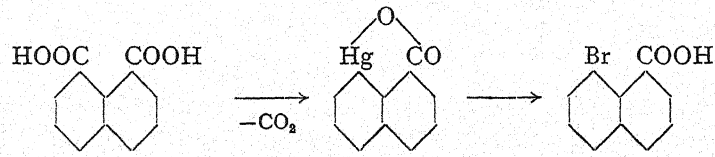
acid on the naphthols, hence they may also be considered as *nitroso-naphthols*. Here we have a case of tautomerism analogous to that of the nitrosophenols.[1] The α-quinone only yields one monoxime.

The two monoximes of β-naphthaquinone differ from the oxime of α-naphthaquinone in their ability to act as mordant dyes, forming dark green lakes with ferric oxide. In particular, the iron salt of α-nitroso-β-naphthol-sulphonic acid is employed in wool-dyeing under the name of *Naphthol Green*. α-Nitroso-β-naphthol precipitates various metals from their solutions, yielding, for example, a sparingly soluble cobaltic compound which may be utilised in separating nickel and cobalt.

Amphi-naphthaquinone (formula, see p. 541) is formed when 2:6-dihydroxy-naphthalene, suspended in benzene, is oxidised with lead peroxide.[2] It crystallises in small yellowish red prisms and is very unstable towards water, alcohol, acids and alkalis. In physical properties it resembles the *o*-quinones. Like the benzoquinones, it is distinguished by a tendency to change into the benzenoid type.

The *amphi*-compound differs from α- and β-naphthaquinones in its far stronger oxidising action. It is truly naphthaquinonoid, whereas the α- and β-isomerides are not completely quinonoid in structure. Here a distinction is drawn between quinones in which the benzene ring or condensed double ring of naphthalene is completely quinonoid and those in which a quinonoid double bond is also part of an aromatic nucleus.

In formation and properties the *naphthalene carboxylic acids* resemble the corresponding acids of benzene, to which reference should be made. **α-Naphthoic acid**, naphthalene α-carboxylic acid, $C_{10}H_7.COOH$, is formed by the action of carbon dioxide on naphthyl magnesium bromide, or from sodium naphthalene-α-sulphonate by distillation with sodium cyanide followed by hydrolysis of the resulting naphthonitrile. It melts at 160°, and at higher temperatures loses carbon dioxide to yield naphthalene. *α-Naphthaldehyde* may be prepared by a modification[3] of Gattermann's synthesis using naphthalene, hydrogen cyanide and aluminium chloride in chlorobenzene as solvent. **β-Naphthoic acid** melts at 182°. **Naphthalic acid**, naphthalene 1 : 8-dicarboxylic acid, $C_{10}H_6(COOH)_2$, is prepared from acenaphthene by oxidation with sodium bichromate and sulphuric acid. When heated to a high temperature it yields an anhydride resembling phthalic anhydride. Naphthalic acid

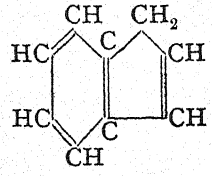


when boiled in neutral solution with mercuric acetate yields a mercuri-anhydride, which with bromine is converted into **8-bromo-naphthoic**

[1] C. H. Sluiter, *Ber.*, 1911, **44**, 1327. [2] R. Willstätter and Parnas, *Ber.*, 1907, **40**, 1406.
[3] L. E. Hinkel, E. E. Ayling and J. H. Benyon, *J. C. S.*, 1936, 340.

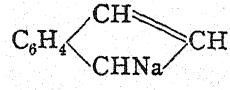
acid.[1] The latter is a useful compound for the synthesis of anthanthrones (*q.v.*).

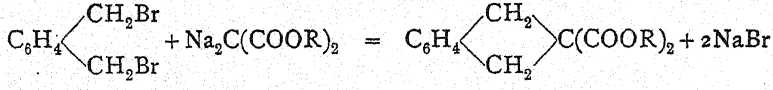
Among other derivatives of naphthalene may be mentioned **acenaphthene** or *peri*-ethylene-naphthalene, $C_{10}H_6\begin{cases}CH_2\\ |\\ CH_2\end{cases}$, m.p. 95°, b.p. 277°, which is found in coal tar. On careful oxidation with sodium bichromate it is converted into acenaphthene-quinone, $C_{10}H_6\begin{cases}CO\\ |\\ CO\end{cases}$, m.p. 261°, naphthalic acid being formed at the same time. Acenaphthene may be prepared synthetically by treating α-bromoethyl-naphthalene, $C_{10}H_7.CH_2.CH_2Br$, with alcoholic potash.


Indene.

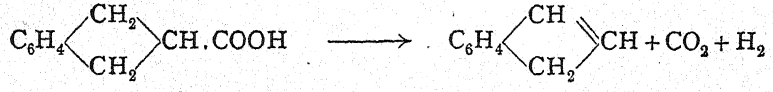
Indene.—As will be seen from the annexed formula, indene contains a benzene nucleus condensed with a cyclo-pentadiene ring. It is present in coal tar, and may be isolated from the "heavy oil" by fractionation and subsequent precipitation with picric acid. A simpler method is to heat the crude indene with sodium at 140° to 150°, when **sodium indene** is formed as a glassy mass. This on treatment with water yields very pure indene.[2] It is a colourless oil, b.p. 178°.

Indene and its derivatives may be obtained synthetically by a number of reactions (see p. 542). Thus *o*-xylylene bromide and sodio-malonic ester combine to form *hydrindene dicarboxylic ester*,





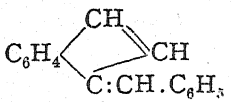
which by hydrolysis and elimination of carbon dioxide can be converted into *hydrindene carboxylic acid*. When the barium salt of the latter is distilled it yields indene[3]:

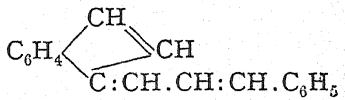


The chief properties of indene depend on the reactivity of the two hydrogen atoms of the CH_2-group (*cf.* fluorene). If indene is heated with alkyl halides in the presence of alkali, these hydrogen atoms are replaced by alkyl groups, and in the condensation of indene with aldehydes they unite with the aldehydic oxygen to form water.[4]

[1] H. G. Rule and A. J. G. Barnett, *J. C. S.*, 1932, 176. F. C. Whitmore and A. L. Fox, *J. A. C. S.*, 1929, 51, 3363; G. J. Leuck, R. P. Perkins and Whitmore, *ibid.*, p. 1831. [2] Weiszgerber, *Ber.*, 1909, 42, 569; 1911, 44, 1436. [3] For the preparation of indene derivatives from phthalic aldehyde see J. Thiele and Falk, *Ann.*, 1906, 347, 112, and from unsaturated ketones, Thiele and Ruggli, *Ann.*, 1912, 393, 61. [4] For further details see Thiele, *Ann.*, 1906, 347, 249.

In this manner benzaldehyde and indene yield *benzylidene-indene* (I) and hydroxy-benzyl-indene, while cinnamic aldehyde and indene give *cinnamylidene-indene* (II).

I. 

II. 

Indene readily takes up oxygen from the air and has a strong tendency to polymerise. With nitric acid it is oxidised to phthalic acid, and on reduction with sodium and alcohol, or more simply by catalytic hydrogenation,[1] it is converted into *hydrindene*, C_9H_{10}.

STRAINLESS RINGS AND CONDENSED RING STRUCTURES

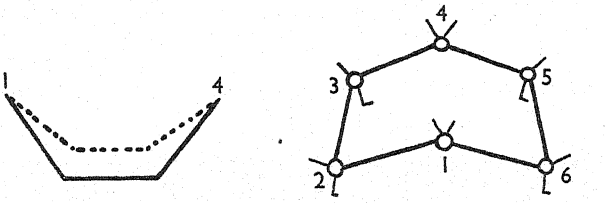
For many years following the introduction of Baeyer's Strain Theory, ring structures were represented as being planar in configuration. Large rings containing seven or more ring atoms were supposed to be unstable and to exist in a condition of strain, due to the distortion of the valency bonds from the normal angle of 109°. From 1925 onwards these ideas were modified by the work of Ruzicka on stable large ring compounds such as muscone and civetone (p. 356), and by Hückel's investigations on the decalins and hydrindanes.

A **theory of strainless rings** in which the tension is relieved by deviations from the plane model was put forward as early as 1892 in a mathematical paper by Sachse,[2] and revived in a more definite form in 1918 by Mohr.[3] The theory may be summarised as follows. Rings containing 3, 4 and 5 carbon atoms must have a plane configuration, because this results in the least possible distortion from the normal valency angle. On the other hand, a ring containing 6 or more carbon atoms may become completely strainless by assuming a puckered or folded form.

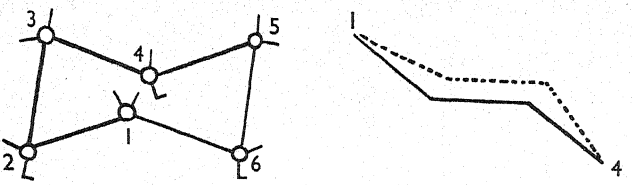
6-Membered Rings.—Two models are possible on the tetrahedral basis, as represented on following page,[4] in the non-rigid *boat or trough form* and the semi-rigid *chair form*. At first sight atoms 1 and 4 in the boat form appear to stand in a special relationship to one another, but this is not the case. An examination of the actual model shows that the ring bonds are mobile, enabling the 1 : 4-positions to pass successively into the 2 : 5-, 3 : 6- and so back to the original 1 : 4-arrangement. The chair model is semi-rigid and cannot merge into the boat form without definite strain being put upon the bonds. This strain, however, is considerably smaller than that required to maintain the six carbon atoms in one plane. Mohr concludes that in practice these two structures represent only one compound, in agreement with our present knowledge of cyclohexane and its derivatives.

[1] J. v. Braun and Kirschbaum, *Ber.*, 1922, **55**, 1680. [2] *Ber.*, 1890, **23**, 1363; *Zeit. physik. Chem.*, 1892, **10**, 203. [3] *J. prakt. Chem.*, 1918 [2], **98**, 349; 1922, **103**, 316. [4] In these diagrams the models may be pictured as being supported on a table by the bonds drawn as a letter L.

Fusion of Two Six-membered Rings.—The most important developments of the Sachse-Mohr theory of strainless rings have arisen from its application to saturated condensed ring systems. Mohr in 1918 was the first to suggest that two buckled cyclohexane rings could be condensed together by either *cis* or *trans* linkages, yielding two decahydronaphthalenes. In addition each ring could exist theoretically in boat and

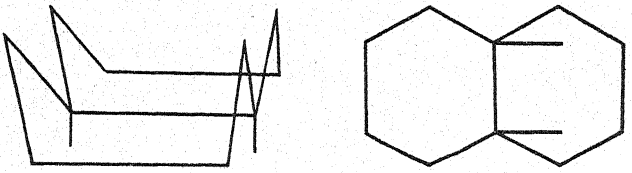


Boat or trough form.

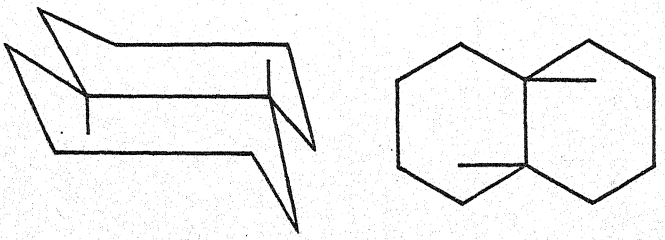


Chair form.

chair forms, but in practice these easily pass into one another. The two *cis* and *trans* **decalins** (decahydronaphthalenes), however, should be stable compounds as shown in the following formulæ, where the positions of the hydrogen atoms attached to the two common carbon atoms are indicated by bonds. On Baeyer's hypothesis each ring must exist in a plane form, leading to a *cis* decalin as the only possible structure.



cis-Decalin.



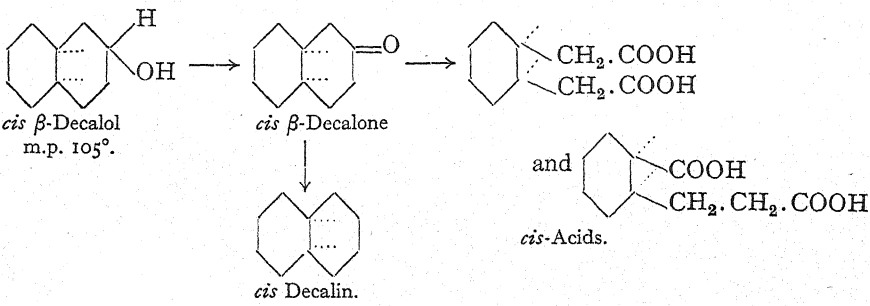
trans-Decalin.

Seven years later, in 1925, the existence of two decalins was established experimentally by Hückel,[1] who started from the two known forms of

[1] *Ann.*, 1925, **441**, 1; *Ber.*, 1925, **58**, 1449.

β-decalol (decahydro-β-naphthol). These two compounds, m.p. 105° and 75° respectively, had been isolated by earlier workers from the reduction products of β-naphthol, although the nature of their isomerism was not known.

Hückel found that on oxidation with potassium dichromate and acetic acid each β-decalol gave rise to a different β-decalone, a fact which could be explained on Mohr's theory but not on the basis of a plane ring structure. Each decalone was reduced to a decalin by use of amalgamated zinc and hydrochloric acid (*Clemmensen* method), and each decalol was converted by oxidation with cold acid permanganate solution into a mixture of cyclohexane-1 : 2-diacetic acid and cyclohexane-1-carboxy-2-propionic acid. These two acids as obtained from β-decalol, m.p. 105°, were of the *cis* configuration. This decalol and the related decalone and decalin are therefore also of *cis* structure.



cis β-Decalol m.p. 105°. *cis* β-Decalone. *cis*-Acids. *cis* Decalin.

The other series of compounds prepared from β-decalol, m.p. 75°, were proved in a similar manner to possess *trans* structures. The physical properties of the two decalins are given below :

trans Decalin : m.p. −36°, b.p. 185°, d_4^{20} 0·872, n_D^{20} 1·4713.

cis Decalin : m.p. −51°, b.p. 193°, d_4^{20} 0·898, n_D^{20} 1·4823.

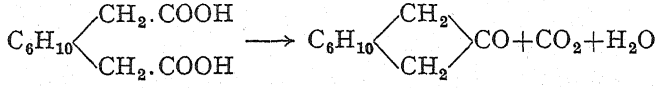
The same two decalins were also isolated by careful fractionation of the mixture obtained from the direct hydrogenation of naphthalene. They are stable compounds, although *cis* decalin is slowly and almost quantitatively isomerised into *trans* decalin at room temperature in contact with aluminium chloride, a reagent which is known to loosen the carbon bonds. The lower stability of the *cis* form under these conditions is in agreement with its somewhat greater heat of combustion.

It may be noted that β-decalol has three asymmetric carbon atoms, an additional possibility of isomerism having been introduced owing to the *cis* and *trans* arrangement of the CHOH-group with respect to the decalin residue. All four of the expected racemic forms were isolated by Hückel,[1] by reduction of the *cis* and *trans* β-decalones. Reduction of the oximes of the decalones resulted in the separation of four racemic β-amino-decalins.

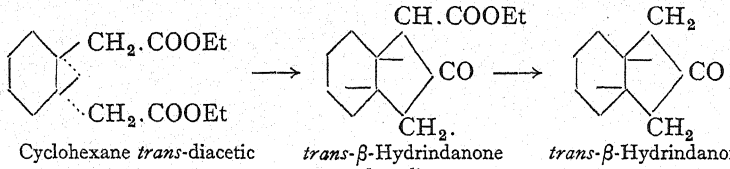
[1] *Ann.*, 1927, 451, 109.

Fusion of a Six- with a Five-membered Ring.—Theoretically a plane five-membered ring can only be attached to cyclohexane to form a strainless compound if the union is by *cis* linkages. On the assumption of buckled rings, however, the tension arising from *trans* coupling is not great.

Hückel [1] has made a careful study of the **hydrindane system** and isolated both *cis* and *trans* **hydrindanones.** The structures of these compounds follow from their mode of formation from *cis* and *trans* cyclohexane-diacetic acids by distillation with acetic anhydride,



or from the corresponding esters by an internal acetoacetic ester condensation in the presence of sodium ethoxide, followed by hydrolysis with mineral acid and loss of carbon dioxide. Thus with the *trans* ester,



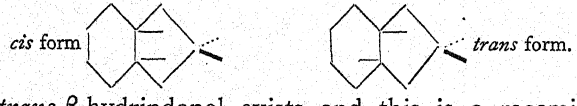
Cyclohexane *trans*-diacetic ester

trans-β-Hydrindanone α-carboxylic ester

trans-β-Hydrindanone.

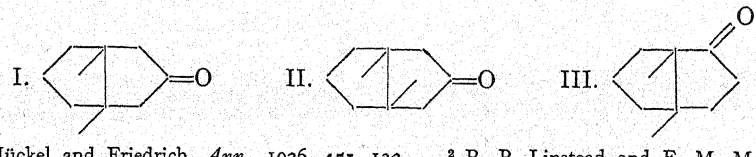
trans-β-Hydrindanone is more stable than the *cis*-compound and has a lower heat of combustion. This is not in agreement with theoretical conclusions, and led Hückel to suggest that the strain theory cannot be applied in a simple manner to a bicyclic system.

The above configurations were also confirmed by reducing the ketones to the **hydrindanols** (CO ⟶ CHOH). As was to be expected from the models, *cis* β-hydrindanol occurs in two geometrical isomerides, each of which possesses a plane of symmetry containing the H and OH groups.



Only one *trans*-β-hydrindanol exists and this is a racemic compound which can be resolved into two optically active forms.

Fusion of Two Five-membered Rings.—Theoretical considerations suggest that any deviation from the plane model in either 5-ring will result in tension and that only fusion in the *cis* position will give a stable compound. This is borne out by the work of Linstead, Meade and Cook [2] on the **bicyclo-octanones.** These compounds were prepared from the *cis* and *trans* cyclopentane-diacetic acids, $C_5H_8(CH_2.COOH)_2$. Of the



[1] Hückel and Friedrich, *Ann.*, 1926, **451**, 132. [2] R. P. Linstead and E. M. Meade, *J. C. S.*, 1934, 935; A. H. Cook and Linstead, *ibid.*, p. 946.

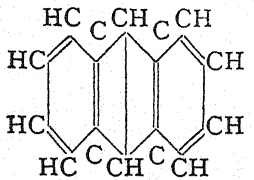
cis and *trans* β-bicyclo-octanones (I and II), the former is the more readily obtained and is the more stable. *cis* α-Bicyclo-octanone (III) was the only α-ketone which could be isolated, as the *trans* isomeride is apparently converted into the *cis* form under the influence of heat.

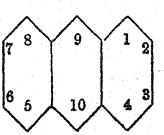
Similar stability relationships exist among anhydrides of this type. Thus the anhydride of *cis* cyclopentane-1-carboxy-2-acetic acid is more stable than that of the *trans* compound.[1]

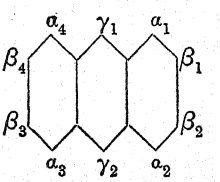
XV

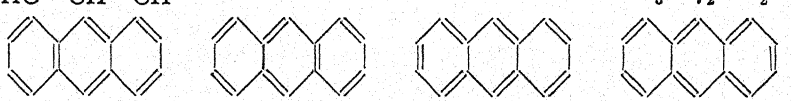
Anthracene Group

Anthracene, $C_{14}H_{10}$, is the parent substance of a number of interesting compounds and valuable dye-stuffs. It is present to the extent of 0·25 to 0·45 per cent. in coal tar, and distils over in the anthracene oil, boiling above 270°. In this it is mixed with various products such as phenanthrene, chrysene, carbazole and paraffins, which are difficult to remove. Crude anthracene crystallises out from the mixture on cooling and is separated in filter presses. The product, which contains about 30 to 50 per cent. of anthracene, is purified by treatment with pyridine bases or solvent naphtha, when most of the phenanthrene, fluorene and other impurities pass into solution, leaving an 80 to 90 per cent. anthracene. The latter is obtained in finely-divided form by sublimation or distillation in steam, and if required for the preparation of dyes is then worked up directly into anthraquinone. Commercial crude anthracene may be further purified in a number of ways, *e.g.* by treatment with liquid sulphur dioxide, in which the impurities dissolve.

I. 

II*a*. 

II*b*. 

III. 

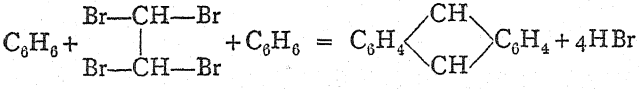
Pure anthracene, m.p. 213°, b.p. 351°, crystallises in colourless plates having a blue fluorescence. It dissolves readily in hot benzene, with difficulty in alcohol and ether, and is insoluble in water. Picric acid combines with it to form an addition compound, $C_{14}H_{10},C_6H_2(NO_2)_3OH$, crystallising in red needles, m.p. 138°. Graebe and Liebermann represented anthracene by formula I consisting of three condensed benzene nuclei, the central one having a para linkage. Although supported by synthesis, this structure has now been abandoned owing to the abnormal

[1] R. P. Linstead and E. M. Meade, *J. C. S.*, 1934, 935; A. H. Cook and Linstead, *ibid.*, p. 946.

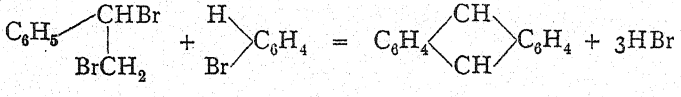
length of the central link and the molecular strain which would result from its formation, since X-ray analysis has shown that all the carbon atoms in anthracene lie on the same plane. The modern view is that the anthracene molecule is in a state of resonance (see p. 88), the four principal contributing forms being shown in III.

Anthracene is formed by the following reactions :

1. By heating benzene with symmetrical tetrabromo-ethane in the presence of aluminium chloride (Anschütz).

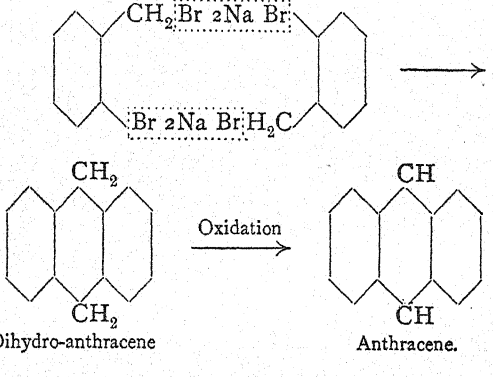


2. In a similar manner, by the action of aluminium chloride on a mixture of $\alpha\beta$-dibromo-ethyl-benzene and bromo-benzene.[1]

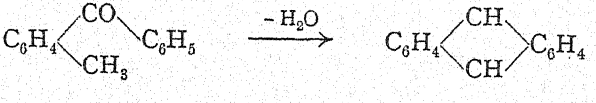


These two syntheses prove that the middle group, C_2H_2, of anthracene is linked to two benzene nuclei, but give no information as to the actual points of union.

3. Anthracene, however, is also formed when *o*-bromo-benzyl bromide is treated with sodium. Hence it follows that the middle group is attached to two *o*-carbon atoms of each benzene ring. In this reaction the first product is dihydro-anthracene, which is readily converted into anthracene by oxidation.



4. Anthracene is also obtained by heating *o*-tolyl phenyl ketone with zinc dust.



A number of other syntheses of anthracene have also been effected. Synthetic methods of preparing anthraquinone, and the formation of anthracene from this compound and from alizarin, are described later.

[1] Schramm, *Ber.*, 1893, **26**, 1706.

Derivatives of Anthracene

Anthracene [1] behaves in the same manner as naphthalene on *hydrogenation.* Reduction with sodium and alcohol results in the addition of two hydrogen atoms to the " middle group," with formation of *dihydro-anthracene.* Energetic reduction with phosphorus and hydriodic acid yields *hexahydro-anthracene*, $C_{14}H_{16}$, and *anthracene perhydride*, $C_{14}H_{24}$. Catalytic hydrogenation under pressure leads to the production of *octa-hydro-anthracene*, $C_{14}H_{18}$, m.p. 73°, which is also readily prepared on the technical scale.[2]

Numerous substitution products of anthracene are known, the position of the substituents being indicated by numbers or letters as given in formulæ II*a* and II*b* on p. 549. These formulæ also illustrate the large number of structural isomerides possible. Substitution in the middle group leads to the formation of γ- or *meso*-derivatives. According to theory there should be three isomeric monosubstitution products in every case. Only the most important of these compounds will be described here.

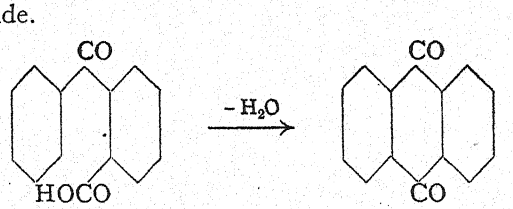
The action of chlorine or bromine on anthracene leads first to the formation of *γ-mono-* and *di-halogen* derivatives.

Nitric acid very readily oxidises anthracene to *anthraquinone.* On the other hand, nitric acid reacts with anthracene in glacial acetic acid solution in the presence of acetic anhydride to form 9-*nitro-anthracene.* This compound is more conveniently prepared by an indirect method described later.

Anthracene-sulphonic acids can be obtained by the sulphonation of anthracene, or by the reduction of anthraquinone-sulphonic acids.

Hydroxy-anthracenes, which resemble the phenols and naphthols in their behaviour, are formed by fusing anthracene-sulphonic acids with alkali, and by the reduction of anthraquinone and its substitution products. The meso-phenols of the anthracene series, *anthranol* and *anthra-hydro-quinone*, exhibit tautomerism.[3]

Anthraquinone, $C_6H_4(CO)_2C_6H_4$, is obtained synthetically when *o*-benzoyl-benzoic acid is heated with phosphorus pentoxide. This acid can be prepared by heating phthalic anhydride with benzene and aluminium chloride, or by the action of phenyl magnesium bromide on phthalic anhydride.



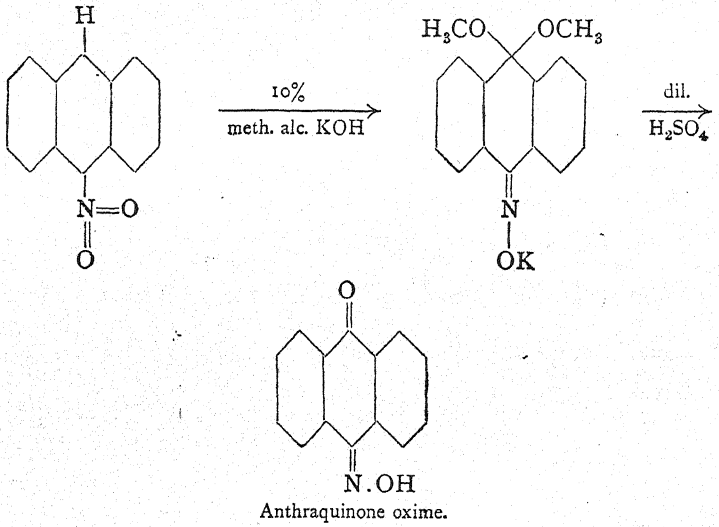
o-Benzoyl-benzoic acid — Anthraquinone.

Anthraquinone is prepared industrially in large quantities for the

[1] For a synthesis of anthracene from a naphthalene derivative, see W. A. Noyes and Colver, *J. Am. C. S.*, 43, 898. [2] G. Schroeter, *Ber.*, 1924, 57, 2003; 1927, 60, 2035. [3] K. H. Meyer, *Ann.*, 1911, 379, 37.

manufacture of alizarin, by oxidising 90 per cent. anthracene with sodium bichromate and sulphuric acid. The product so obtained may be freed from impurities derived from the phenanthrene, fluorene, etc., present in crude anthracene, by dissolving it in hot concentrated sulphuric acid, in which anthraquinone dissolves unchanged while the original impurities or their oxidation products are converted into water-soluble sulphonic acids. Hence, on diluting the acid solution with water, only anthraquinone is precipitated. It may be further purified by distillation in steam or by treatment with pyridine.

Anthraquinone melts at 285°, boils at 382°, and crystallises in yellow needles or prisms which readily sublime. It is a very stable compound, and is only attacked with difficulty by nitric acid and oxidising agents. In its whole behaviour it stands much closer to the diketones than to the quinones, possessing neither the characteristic pungent smell of quinone nor its property of being reduced to hydroquinone with sulphurous acid. With hydroxylamine it yields bright yellow needles of *anthraquinone oxime*, which decompose at 224°. According to Meisenheimer,[1] the



Anthraquinone oxime.

oxime is also formed from 9-nitro-anthracene by boiling with methyl alcoholic potash and subsequent treatment with dilute mineral acid (*cf.* p. 535).

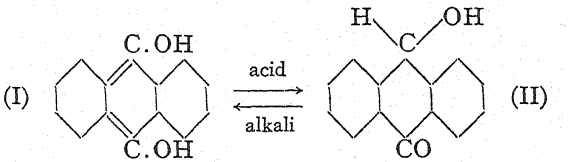
This reaction is of general significance in so far that the "*oxime transformation*" of α-unsaturated nitro-compounds under the influence of alkali appears to be a comparatively common property of this class of compound.

On fusion with potassium hydroxide anthraquinone breaks up to give two molecules of benzoic acid.

Reduction of Anthraquinone.—On reduction in alcoholic suspension

[1] *Ann.*, 1902, **323**, 205; 1907, **355**, 249.

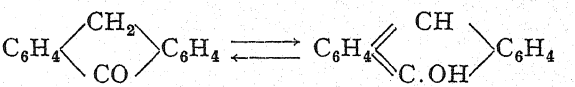
with sodium hyposulphite, or by warming with zinc dust and alkali, anthraquinone is converted into **anthra-hydroquinone** (I), which is tauto-



meric with **oxanthranol** (II). Both forms may be isolated according to the experimental conditions.

Oxanthranol (or anthrahydroquinone) is an unstable substance which gives a beautiful and striking reaction sometimes used as a *test for anthraquinone*. The greenish-yellow compound dissolves in alkali, giving a blood-red colour; on shaking with air, however, the red solution is very rapidly decolorised and yellow anthraquinone separates. The alkaline solution has been shown to contain a considerable amount of hydrogen peroxide (or alkali peroxide).[1]

More vigorous reduction of anthraquinone with tin and hydrochloric acid yields **anthrone,** m.p. 155° (decomp.). It is a relatively stable colourless compound and non-fluorescent. When dissolved in warm alkali and precipitated by acids, it is obtained in the tautomeric form of **anthranol.**[2] The latter is a yellow-brown very unstable compound, which



Anthrone Anthranol.

melts at 120° if the melting-point tube is dipped rapidly into a bath at that temperature; if determined in the ordinary way the compound softens at 120° and only melts completely about 154°, owing to its rapid isomerisation into anthrone. Anthranol forms blue fluorescent solutions. From either compound in organic solutions an equilibrium mixture containing a large proportion of anthrone is obtained. Anthrone is an intermediate in the preparation of benzanthrone.

Finally, by heating with phosphorus and hydriodic acid in a closed tube, or by distillation with zinc dust, anthracene may be obtained.

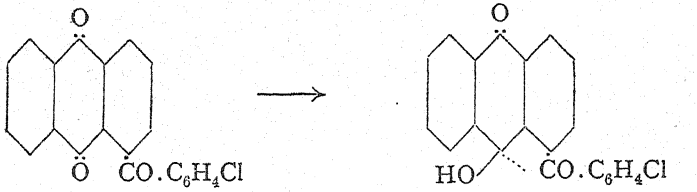
Anthraquinone can be brominated, nitrated and sulphonated.

Oxanthronyls. Compounds containing Trivalent Carbon

When α-benzoylated anthraquinones are treated with aluminium or copper in concentrated sulphuric acid, or with zinc dust and ammonia, they are converted into remarkable compounds distinguished by a deep, violet-blue colour, and the magnificent fluorescence of their solutions in certain organic solvents. These compounds, which have been termed

[1] Manchot, *Ann.*, 1901, **314**, 179. [2] K. H. Meyer, *Ann.*, 1911, **379**, 39.

benzoyl-oxanthronyls, represent a new class containing trivalent carbon and are comparatively stable.[1]



1-*p*-Chlorobenzoyl-anthraquinone — 1-*p*-Chlorobenzoyl-9-oxanthronyl.

They are insoluble in alkali, form deep green sulphates with concentrated sulphuric acid, and their solutions gradually become decolorised on long standing in air and light, particularly in the presence of water. With alkaline hydrosulphite they undergo further reduction.

There are now several classes of compounds known containing trivalent carbon, including the *triaryl-methyls* discovered by Gomberg, the *metallic ketyls* of Schlenk, and the above *benzoyl-oxanthronyls*.

Anthraquinone Sulphonic Acids

The sulphonation of anthraquinone provides a striking illustration of the manner in which the course of a reaction may at times be influenced by the addition of an apparently indifferent substance (compare p. 452, on the conversion of naphthalene into phthalic acid). Sulphonation in the ordinary way only yields β-sulphonic acids, together with an exceedingly small quantity of α-acids. On the other hand, the presence of a small amount of mercury so favours the formation of α-sulphonic acids that the product of reaction is almost pure α-acid. This action of mercury practically brings about a complete displacement of the normal position of substitution, and also enables the reaction to be carried through much more easily. It is therefore of great value industrially since anthraquinone sulphonic acids are important intermediates in the preparation of dyestuffs.

The catalytic influence of mercury does not appear to be limited to sulphonation, but extends to nitration and probably also to other substitution reactions of anthraquinone. So far as has been observed, however, this effect is peculiar to anthraquinone derivatives.

Another method of preparing α-anthraquinone sulphonic acids is to heat α-nitro-anthraquinones with aqueous solutions of neutral alkali sulphites, when the nitro-group is readily exchanged for the sulphonic group. Thus α-nitro-anthraquinone yields **anthraquinone α-sulphonic acid,** and the 1:5- and 1:8-dinitro-derivatives give the corresponding **1:5-** and **1:8-disulphonic acids.** In these α-sulphonic acids the acid group is comparatively reactive. When heated with milk of lime they are converted into *hydroxy-anthraquinones*, and with ammonia or primary amines they yield the corresponding *amino-anthraquinones*. On being

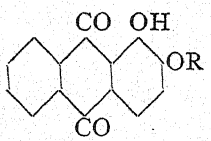
[1] R. Scholl, *Ber.*, 1921, 54, 2376; 1925, 56, 918, 1065, 1633.

heated with potassium phenoxide the α-sulphonic acids yield *phenyl ethers of hydroxy-anthraquinones*. Reduction with zinc dust and ammonia converts anthraquinone-α-monosulphonic acid into *anthracene α-sulphonic acid*, which on fusion with alkali gives *α-anthrol*. The nitration of anthraquinone α-sulphonic acid leads to the formation of two **nitro-anthraquinone sulphonic acids**, with the substituents in the 1:5- and 1:8-positions respectively. These are readily reduced to **1:5** and **1:8-amino-anthraquinone sulphonic acids**, which can be diazotised and coupled with phenols and amines. When heated with methylamine these amino-acids exchange the sulphonic group for the residue —NH.CH_3, with the production of 1:5- and 1:8-*monomethyl-diamino-anthraquinones*, $C_{14}H_{16}O_2\langle^{NH.CH_3}_{NH_2}$. It is obvious that a great number of anthraquinone derivatives can be prepared by such methods.

Hydroxy-anthraquinones

Hydroxy-anthraquinones can also be prepared from chloro- and bromo-anthraquinones by fusion with alkali, and further by the anthraquinone synthesis mentioned on p. 551, using phenols in place of benzene, *i.e.*, by heating phthalic anhydride with mono- or dihydric phenols in the presence of aluminium chloride. A reaction of practical value is the formation of polyhydroxy-anthraquinones by oxidising anthraquinone or its simple hydroxy derivatives by means of hot fuming sulphuric acid. The addition of a little boric acid considerably increases the yield.

Alizarin, 1:2-*dihydroxy-anthraquinone*, $C_{14}H_6O_2(OH)_2$, is the most important hydroxy derivative. It ranks with indigo as the most valuable of all dye-stuffs, whether synthetic or natural. Prior to 1869 it was exclusively prepared from madder root. *Madder* (Rubia tinctorum) is a shrub growing to about three feet in height, which was cultivated more especially in France. It contains in its root a number of glycosides such as *ruberythric acid*, *rubianic acid* and *rubian*. *Ruberythric acid* is an alizarin derivative of the annexed formula,[1] where R is a residue of the disaccharide primverose (a *d*-xylosido-*d*-glucose). On hydrolysis with hot dilute sulphuric acid it yields alizarin, *d*-xylose and *d*-glucose. *Rubianic acid*, on the other hand, is hydrolysed to purpurin (1:2:4-trihydroxy-anthraquinone) and carbohydrate(s).

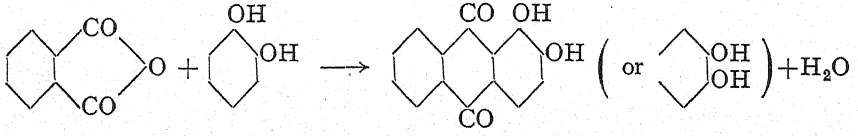


For dyeing, the ground root of madder, containing about 1 per cent. of dye-stuffs, or the prepared mixture of dyes (*garancin*) was formerly employed.

Constitution of Alizarin.—In 1865 Graebe and Liebermann obtained the hydrocarbon anthracene by distilling natural alizarin with zinc dust.

[1] Jones and Robertson, *J. C. S.*, 1933, 1167; D. Richter, *ibid.*, 1936, 1701.

This fact, together with the discovery of the method described below of preparing alizarin artificially, pointed to the compound being an anthraquinone derivative in which two hydrogen atoms were replaced by two hydroxyl groups. The formation of phthalic acid by the oxidation of alizarin [1] proved that both hydroxyl groups were contained in the same benzene nucleus, and the synthesis of alizarin (accompanied by *hystazarin*, now known to be 2 : 3-dihydroxy-anthraquinone) from phthalic anhydride and pyrocatechol showed them to be in the *o*-position to one another.

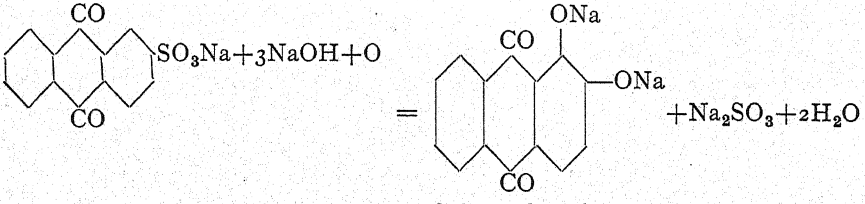


Phthalic anhydride. Pyrocatechol. Alizarin.

Finally, the existence of two isomeric nitro-alizarins having the nitro-group in the same benzene nucleus as the hydroxyl groups is a proof that the hydroxyl groups occupy the 1 : 2- and not the 2 : 3-positions.

Technical Preparation of Alizarin.—Graebe and Liebermann were the first to prepare alizarin artificially. They obtained it by fusing dibromo-anthraquinone with potassium hydroxide, a method not adapted to large scale practice. The industrial preparation was only established successfully when W. H. Perkin in England and Caro, Graebe and Liebermann in Germany simultaneously substituted the cheaper anthraquinone sulphonic acids for the expensive dibromo-anthraquinone. It was at first believed that the sulphonation of anthraquinone led to the formation of a disulphonic acid, which then yielded alizarin on fusion with alkali. Perkin, however, proved that the essential product was the β-monosulphonic acid, so that the additional hydroxyl group introduced into the adjacent α-position during the fusion must be the result of aerial oxidation. Two years later, in 1873, Koch obtained an increased yield of alizarin by adding the calculated amount of an oxidising agent (sodium nitrate or chlorate) to the melt, which is the manner in which the technical preparation is still conducted. The process is carried out as follows.

Equal amounts of anthraquinone and 40 per cent. oleum are heated at 160° to 170°, in an iron vessel provided with stirring apparatus,



Sodium salt of alizarin.

when the greater part of the anthraquinone is converted into the β-monosulphonic acid. On pouring the melt into water any unchanged

[1] For the oxidation of alizarin in alkaline solution see R. Scholl, *Ber.*, 1918, 51, 1419; 1919, 52, 1142, 1829.

anthraquinone separates out. This is filtered off, and the sulphonic acid is precipitated from the filtrate as the sparingly soluble sodium salt by the addition of soda. The salt is then fused with sodium hydroxide and the requisite amount of sodium nitrate.

The fusion is effected under pressure in horizontal iron cylinders provided with stirring apparatus, at about 180° to 185°. The fused mass is dissolved in water and alizarin precipitated as orange yellow flakes by the addition of sulphuric acid. It is separated in filter presses, mixed with water to a 20 per cent. paste and placed in this form on the market.

100 parts of coal tar containing 0·6 parts of anthracene yield 0·6 parts of alizarin.

The artificial preparation of alizarin was the first synthesis of a valuable natural dye-stuff to be successfully carried out on the industrial scale. Synthetic alizarin has completely displaced the natural product from the market, and has not only led to the decay of madder cultivation in the Mediterranean countries, but has brought about great changes in the occupation of the people in these parts. Districts which used annually to produce valuable supplies of madder have now reverted to ordinary agricultural pursuits.

Properties and Use of Alizarin.—In the pure state alizarin crystallises in beautiful red prisms or needles, melting at 289°. It is readily soluble in alcohol and ether, but only dissolves sparingly in water, even when heated. Alkalis dissolve it with production of a deep violet red solution. Alizarin yields insoluble coloured "lakes" with mordants; with aluminium and tin oxides the colour is red, with chromium oxide a brownish violet and with ferric oxide a violet black.[1] It is by the aid of these mordants that the alizarin is attached to the fabric, and the lakes, of which aluminium red is the most important, therefore constitute the actual dye-stuffs.

Alizarin and the closely related compounds purpurin, anthrapurpurin and flavopurpurin are typical mordant dyes. They dye both wool and cotton with the aid of mordants, giving colours which are very fast to light and washing. Consequently they are of great value commercially.

Turkey Red Process

In this process the cotton fabric or yarn to be dyed is steeped in an aqueous solution of **Turkey Red oil** and dried. It is then mordanted with aluminium acetate, dried, and dyed in an alizarin bath containing Turkey Red oil and a little chalk. Finally, the material is steamed under pressure and the colour cleared by washing with soap. In this manner there is obtained the fiery Turkey Red, which is very fast to washing, acids and light. The same complex colour lake may be prepared directly by prolonged heating of alizarin, aluminium acetate and calcium acetate

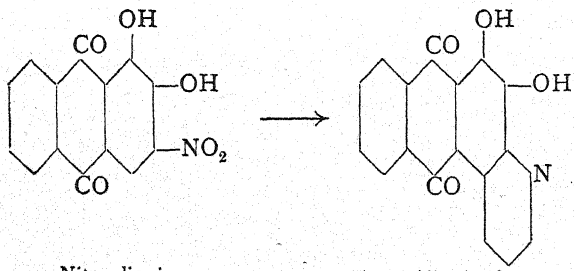
[1] For alizarin-iron lakes see A. W. Bull and J. R. Adams, *J. Phys. Chem.*, 1922, **25**, 660.

in water, and has been shown to contain alizarin, Al and Ca in the proportions 4 : 2 : 3. Five molecules of water are also present, which are essential parts of the structure. No fatty acid is contained in the dye, the only function of the Turkey Red oil used in the dyeing process being apparently to fix the metallic oxides as soaps on the fibre and to deposit the lake in a very finely dispersed state.[1] It is this almost colloidal condition of the dye which is believed to be responsible for the brilliant colour. Calcium may be replaced by certain other divalent metals, *e.g.* tin, and aluminium by trivalent iron.

Turkey Red oil is prepared from castor oil, which contains glycerides of unsaturated fatty acids and of hydroxy-oleic acid, $C_{17}H_{32}(OH).COOH$. Concentrated sulphuric acid is dropped gradually, with stirring, into cooled castor oil, when the latter is hydrolysed and the sulphuric acid partly adds on to the double bonds of the resulting unsaturated acids, and partly esterifies the hydroxy-acid to give a ricinoleic-sulphuric acid, $C_{17}H_{32}\begin{cases}O.SO_2OH\\COOH\end{cases}$. After washing with a solution of sodium sulphate or common salt, the product is neutralised with ammonia, and the liquid, which is then readily soluble in water, is placed on the market as Turkey Red oil.

When brominated in glacial acetic acid solution alizarin readily yields 3-*bromo-alizarin*, m.p. 260° to 261°; with bromine water 3-*bromo-alizarin-quinone* is obtained.[2]

Alizarin gives valuable products on nitration. The resulting *nitro-alizarin*, $C_{14}H_7(NO_2)O_4$, is mainly the β-compound, and is used under



Nitro-alizarin Alizarin blue.

the name of **alizarin orange.** With alumina as mordant it dyes an orange colour. When a mixture of β-nitro- and β-amino-alizarin is heated with glycerol and sulphuric acid (*cf.* quinoline synthesis) it yields **alizarin blue,** which may be used as a substitute for indigo blue in wool and cotton dyeing. Alizarin blue bears the same structural relationship to alizarin as quinoline does to benzene. It is employed in the form of its water-soluble sodium bisulphite compound, which is the *alizarin blue S* of commerce.

Quinizarin, 1 : 4-dihydroxy-anthraquinone, may be obtained by oxidising anthraquinone with fuming sulphuric acid in the presence of boric acid.

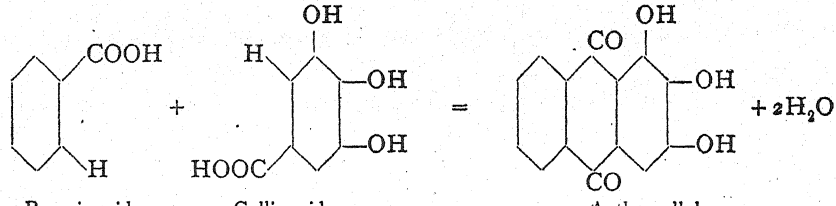
[1] H. E. Fierz-David and M. Rutishauser, *Helv. Chim. Acta*, 1940, **23**, 1298. [2] O. Dimroth, Schultze and Heinze, *Ber.*, 1921, **54**, 3035.

Anthrarufin, 1:5-dihydroxy-anthraquinone, is prepared by heating anthraquinone-1:5-disulphonic acid (see p. 554) with milk of lime at 200°. It is used in the manufacture of *Alizarin Saphirol B.*

Trihydroxy-anthraquinones, $C_{14}H_5O_2(OH)_3$

Some of these compounds are also valuable mordant dyes.

Anthragallol, 1:2:3-*trihydroxy-anthraquinone,* is prepared by heating equimolecular amounts of benzoic acid and gallic acid with concentrated sulphuric acid.



Benzoic acid Gallic acid Anthragallol.

It forms brown lakes with chromium mordants and is used under the name of " alizarin brown " or " anthracene brown."

Purpurin, 1:2:4-*trihydroxy-anthraquinone,* as already stated, is found with alizarin in madder root, and can be obtained by oxidising alizarin with manganese dioxide and sulphuric acid. It is very little used. **Flavopurpurin,** 1:2:6- and **iso-** or **anthra-purpurin,** 1:2:7-trihydroxy-anthraquinones are produced by fusing anthraquinone disulphonates with sodium hydroxide and potassium chlorate. The former gives a scarlet red with aluminium mordant, and the latter a yellower shade of red. They are employed chiefly in cotton printing.

Polyhydroxy-anthraquinones

Polyhydroxy-anthraquinones, which are also of technical interest, may be obtained from anthraquinone or the above hydroxy derivatives by oxidation with sulphuric acid (see p. 555 *et seq.*).

Alizarin Bordeaux, 1:2:5:8-*tetrahydroxy-anthraquinone,* is formed by heating alizarin with fuming sulphuric acid. With a chromium mordant it yields a lake of purple tint. **Alizarin cyanine,** 1:2:4:5:8-pentahydroxy-anthraquinone, $C_{14}H_3O_2(OH)_5$ is obtained by oxidising alizarin bordeaux with manganese dioxide and sulphuric acid. It gives a purple shade of blue with chromium mordant. **Rufigallic acid,** 1:2:3:5:6:7-*hexahydroxy-anthraquinone,* is produced from gallic acid by heating with concentrated sulphuric acid, when 2 mols. of the gallic acid condense with one another (*cf.* anthragallol). It colours a chromium-mordanted fabric brown. **Anthracene blue,** a position isomeride of rufigallic acid, is obtained by heating dinitro-anthraquinone with fuming sulphuric acid. It forms a pure blue chromium lake.

It should be noted that a large number of sulphonic derivatives of the above dyes are also used in the form of their soluble sodium salts, under the name of " alizarin acid dyes," for dyeing woollen goods.

Influence of Ortho-hydroxylation on the Nature of Hydroxy-anthraquinone Dyes.—It has already been emphasised that the formation of insoluble lakes with metallic mordants is of the highest importance for the practical utilisation of hydroxy-anthraquinones in wool dyeing and cotton printing.

Liebermann and Kostanecki have shown that the presence of one hydroxyl group in the above compounds does not confer the property of forming coloured lakes in sufficiently high degree to give a good dye. For this purpose it is necessary to have two hydroxyl groups which must stand in the ortho- or " alizarin " position to one another.[1] Other positions of the hydroxyls either fail to give strong dyeing properties or lead only to improvement with respect to a few special mordants.

It must therefore be assumed that, in the formation of coloured salts of the type of lakes, two hydroxyl groups in adjacent positions are capable of exerting an influence not attained by hydroxyl groups in other positions.

Werner [2] has developed a general theory of mordant dyes, according to which the power of a chemical compound to yield coloured lakes with mordants depends on the formation of inner complex salts. From this point of view mordant dyes contain a salt-forming group and a group capable of producing a co-ordinative linking with the metallic atom, in such relative positions that an inner metallic complex salt may result.

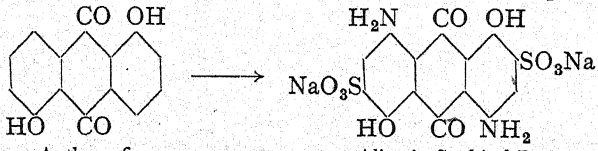
DYESTUFFS OF THE ANTHRAQUINONE GROUP [3]

Under this heading are included many valuable dye-stuffs, which may be divided into three main types.

(a) *Mordant dyes* such as **alizarin, purpurin** and other polyhydroxy anthraquinones already described in the foregoing pages.

(b) *Acid dyes*, which in the form of their sodium salts are absorbed directly on wool to give fast and bright colours. They have very little affinity for cotton even if mordants are used and they form no lakes with tannin. Examples of this kind are the following sulphonated amino-anthraquinones.

Alizarin Saphirol B was the first of this group to be discovered (R. E. Schmidt, 1897). It is prepared from anthrarufin by sulphonating it to

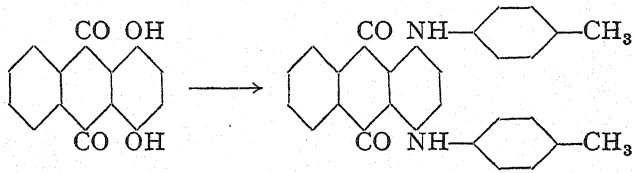


Anthrarufin — Alizarin Saphirol B.

[1] *Ann.*, **240**, 245. *Ber.*, 1887, **20**, 3146; 1889, **22**, 1347; 1893, **26**, 1574; 1901, **34**, 1562, 2344; 1902, **35**, 1497. *Cf.* also Georgievics, *Monats.*, 1911, **32**, 329. [2] A. Werner, *Ber.*, 1908, **81**, 1062. [3] See *The Synthetic Dyestuffs and Intermediate Products*, by Cain and Thorpe, revised by Thorpe and Linstead (Griffin & Co., 1933).

the 2:6-disulphonic acid, followed by nitration in the 4:8-positions and final reduction to the diamino-compound. The sodium salt of the resulting product is Alizarin Saphirol B. It dyes wool a fast blue colour.

Alizarin Cyanine Green (By).—Negative groups in the α-positions in anthraquinone are relatively labile and when quinizarin, its leuco-compound or 1:4-dichloro-anthraquinone is heated with *p*-toluidine the α-substituents are displaced by *p*-toluidine residues to form **Quinizarin Green.** The latter is then disulphonated, when one sulphonic group enters into a position ortho to NH in each toluidine nucleus. The sodium salt of this acid is Alizarin Cyanine Green (By), an acid dye for wool and silk, although it is generally applied with a mordant to give a faster colour.



Quinizarin — Quinizarin Green.

Another similar dye-stuff is **Alizarin Pure Blue B,** which is 1-amino-2-bromo-anthraquinone having a sulphonated *p*-toluidine residue attached to position 4.

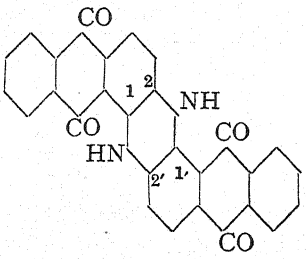
Amino-anthraquinones and their derivatives have been found to be valuable dyes for use with *cellulose acetate silk*, which is not dyed satisfactorily by the majority of the dye-stuffs employed for other textiles.

(c) *Vat dyes,* which are applied chiefly to cotton, include many simple and complex derivatives of anthraquinone, a few examples of which are described in this section.

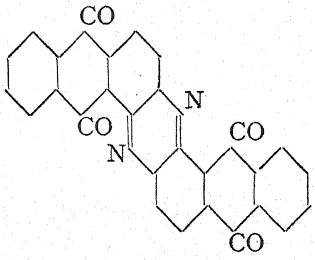
When anthraquinone is treated with reducing agents such as zinc and alkali, it is converted into anthrahydroquinone (see p. 553) which rapidly oxidises back to anthraquinone in air. The reduction product, however, possesses little affinity for the fibre and is of no value in dyeing. On the other hand, certain substituted anthraquinones possess strong colours and yield reduction products which are absorbed by (*i.e.* are substantive to) cotton. These may be employed as dye-stuffs. Thus the benzoyl derivative of 2-amino-anthraquinone, **Algol Yellow WG (By),** is a fast yellow dye. It is used from a weak hyposulphite vat and at low temperatures in order to avoid hydrolysis of the acyl group. A number of more complex compounds built up of several anthraquinone residues linked by imino groups (complex anthraquinonylamines) are also used as dye-stuffs. In the following compound indanthrone, derived from 2-amino-anthraquinone, two molecules of the latter are condensed in such a manner that the imino groups form part of a new six-membered ring.

Indanthrone, Indanthrene Blue, *N-dihydro*-1:2:2′:1′-*anthraquinone-azine.* When β-amino-anthraquinone is fused with potassium hydroxide at 200° to 300°, the potassium salt of a blue hydro-compound is obtained, which on being dissolved in water in the presence of air

deposits the blue dye indanthrone. This dye-stuff is remarkable for the beauty and permanence of the blue shades it produces. From its mode of formation and general behaviour it is assigned the following constitution,[1] according to which it is regarded as a derivative of dihydro-phenazine (described later) :



Indanthrone



Flavanthrone.

Indanthrone is exceedingly stable. Owing to its insolubility it cannot be attached directly to the fibre, but with alkaline hydrosulphite solution it yields a blue reduction product, which is soluble in alkali and extremely sensitive towards atmospheric oxygen. In this form it is brought on to the fabric. It resembles indigo in being a blue *vat dye* (p. 642), and is the first genuine vat dye of the anthracene series. The bath, however, is so strongly alkaline that it cannot be used for dyeing wool, but only for cotton. A number of halogen substitution products and other derivatives of indanthrone (*e.g.* algol blue 3 G, algol green G) are also used extensively as vat dyes.

By conducting the fusion of β-amino-anthraquinone with alkali at the very high temperature of 330° to 350°, dissolving the melt in water in the presence of air and filtering off the alkali-soluble by-products of the reaction, there is formed in place of indanthrone a yellow dye-stuff known as **flavanthrone** [2] or **indanthrene yellow G.** The technical method of preparation is to treat β-amino-anthraquinone with antimony pentachloride in boiling nitrobenzene solution. Indanthrone and flavanthrone are also produced together in variable proportions when β-amino-anthraquinone is treated with acid oxidising agents, such as chromic acid or manganese dioxide and sulphuric acid.

Another substance related to anthracene is **aloïn,** $C_{16}H_{16}O_7$(?), a strong purgative present in aloes, the dried juice of various species of aloe. On heating with zinc dust it yields anthracene, and when oxidised with sodium peroxide gives **emodin,** a 1 : 6 : 8-trihydroxy-3-methyl-anthraquinone.[3]

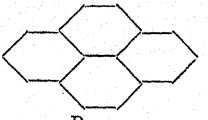
Solubilised Indanthrone.—Indanthrone has to be employed from a strongly alkaline vat, rendering it unsuitable for application to woollen goods, which shrink in contact with alkali. The dye can be adapted for wool and silk by *solubilisation.* Soon after the introduction of the indigosol process (see p. 644), it was discovered by Scottish Dyes, Ltd., that anthra-

[1] R. Scholl, *Ber.*, 1903, **36**, 3410, 3427. See also *Ber.*, 1911, **44**, 1727. [2] R. Scholl, *Ber.*, 1907, **40**, 1691. [3] *Arch. d. Pharm.*, 1911, **249**, 311, 445. *J. pr. Ch.* [2], 1911, **83**, 211. *Helv. Chim. Acta*, 1925, **8**, 26, 140.

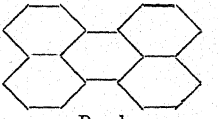
quinone dyes could be converted directly into soluble leuco-esters. For this purpose indanthrone is heated with oleum or chlorosulphonic ester, with the addition of a reducing metal such as zinc, copper or iron, and in the presence of a tertiary base, usually pyridine. The sodium salt of the resulting sulphuric ester is **Solubilised Indanthrene Blue**. In this product two of the keto groups in one anthraquinone residue have been reduced to the leuco state and esterified with sulphuric acid (CO ⟶ C.OH ⟶ C.O.SO_3Na). The other anthraquinone residue is not changed. Solubilised indanthrone is stable in neutral (or alkaline) solution and is absorbed readily by wool, silk and cotton. The dyed material is finally treated with nitrous acid or an acid bichromate solution, which hydrolyses off the sulphuric ester groups and oxidises the resulting leuco-compound back to indanthrone, which is thus firmly embedded in the fibre.

Complex Carbocyclic Quinones [1]

Closely related to anthraquinone are a number of polycyclic quinones, which differ from anthraquinone itself in being highly coloured and in giving reduction products readily absorbed by the fibre. Compounds of this kind which function as vat dyes contain at least two carbonyl groups linked by a conjugated chain of alternate single and double bonds, and include in their molecular structure the characteristic systems of



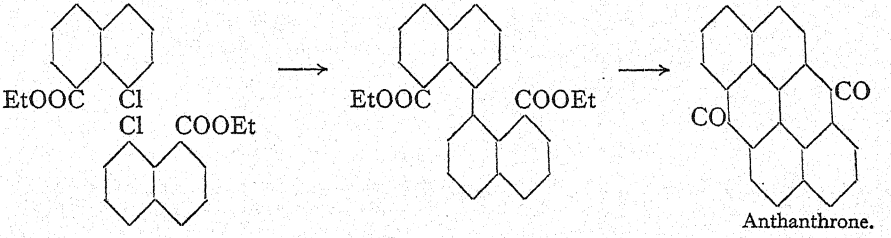
Pyrene



Perylene

pyrene or perylene. Examples of this type are found in anthanthrone and benzanthrone.

Anthanthrone is an orange red compound which does not melt below 300°. It was first prepared by Kalb in 1913 from 8-chloro-1-naphthoic ester. This when heated with copper bronze (*Ullmann reaction*) is converted into 1:1′-dinaphthyl-8:8′-dicarboxylic ester, which on being warmed with concentrated sulphuric acid is cyclised to anthanthrone. Much better yields, however, are obtained by use of 8-bromo-naphthoic



Anthanthrone.

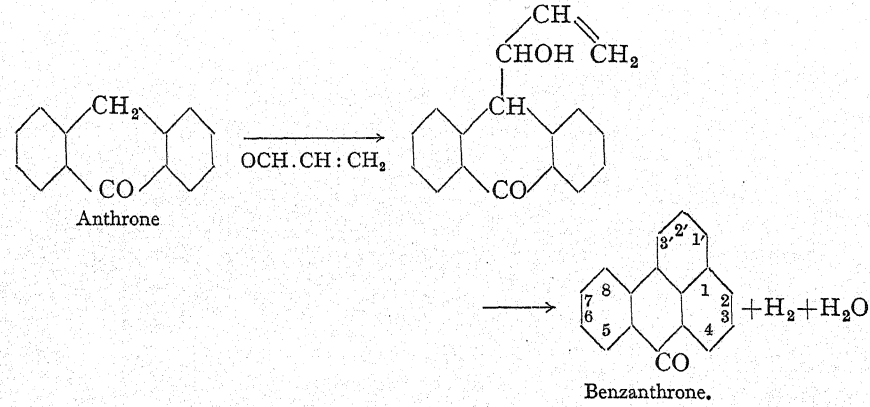
ester [2] (see p. 543). The cyclisation occurs in two stages, one ester group being first hydrolysed to a free carboxyl and rapidly forming a new ketonic ring by condensation with the neighbouring ring. The second

[1] See *The Synthetic Dyestuffs*, by Cain and Thorpe (Griffin, 1933). [2] Rule, Pursell and Brown, *J. C. S.*, 1934, 170.

ester group reacts somewhat more slowly.[1] The half way product having one ketonic ring gives a deep red solution in sulphuric acid owing to the formation of an oxonium salt, and the completion of the reaction is marked by a colour change to green as the second ring is produced to give the diketo compound anthanthrone. Cyclisation may also be effected by converting the ester groups in the dicarboxylic ester into acid chloride groups, followed by treatment with aluminium chloride.

Anthanthrone only dyes a weak yellow, and it is therefore employed as a dyestuff in the form of the more strongly coloured halogen derivatives, *e.g.* **dichloro-anthanthrone (Indanthrene[2] Brilliant Orange)** and **dibromo-anthanthrone (Caledon Brilliant Orange, 4 RS).** Halogen may be introduced directly into anthanthrone, or at the intermediate stage. The compounds give violet vats.

Benzanthrone Colours are prepared from *benzanthrone*, a yellow crystalline compound, m.p. 171°, which is itself of no value as a dye-stuff. Benzanthrone was discovered in 1905 by Bally, who obtained it as a result of heating glycerol and sulphuric acid with anthraquinone. It is now more usual to add copper powder prior to the introduction of glycerol, to effect the reduction of the quinone to anthrone, which is an intermediate in the reaction. The explanation advanced by Bally and Scholl[3] assumes the reduction of some anthraquinone to anthrone, followed by condensation of the latter with acrolein (produced by dehydration of glycerol) to form an aldol, in accordance with the following scheme.



Benzanthrone.

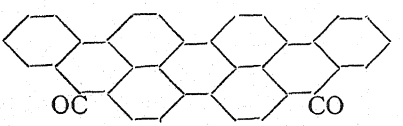
Substituents in the benzanthrone molecule are indicated by a numbering system based on that of anthraquinone, as shown in the formula. On halogenation the compound is attacked first in position 1′. Benzanthrone dissolves in sulphuric acid giving a deep red solution with strong yellow fluorescence.

A deep blue vat dye is prepared from benzanthrone by fusion with

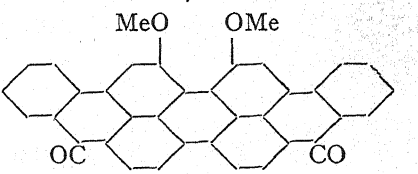
[1] Rule and Smith, *J. C. S.*, 1937, 1099. [2] "Indanthrene" is used as a trade name for the fastest vat dyes produced by the German I.G. combine, and covers a wide variety of chemical types. [3] *Ber.*, 1911, 44, 1656. This mechanism appears to be supported by the work of F. G. Baddar and F. L. Warren, *J. C. S.*, 1938, 401. See also Meerwein, *J. prakt. Chem.*, 1918 (2), 97, 284.

alkali at 240-250°, when two molecules link together at the 1′ and 2 positions with loss of hydrogen to form **dibenzanthrone (Violanthrone, Indanthrene Dark Blue, B.O.).**

A valuable derivative of dibenzanthrone is the dimethoxy compound known as **Caledon Jade Green,** a fine and very fast pale bluish-green colour. This can be prepared by oxidising dibenzanthrone with manganese dioxide and concentrated sulphuric acid at 0°, which introduces



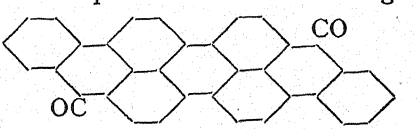
Dibenzanthrone.



Caledon Jade Green.

two hydroxyl groups into the desired positions, followed by methylation in hot nitrobenzene solution with dimethyl sulphate and sodium carbonate. Or benzanthrone can be oxidised to 2′-hydroxy-benzanthrone, using the same reagents, and this methylated to give the methoxy compound. Final mild treatment with potassium hydroxide and alcohol at 180° then yields Caledon Jade Green.

If benzanthrone is first halogenated in the 1′-position and the resulting compound heated with alcoholic potash, condensation occurs with loss of two molecules of hydrogen halide to form **isodibenzanthrone (Isoviolanthrone),** which dyes a more purple colour than its isomeride dibenzanthrone.



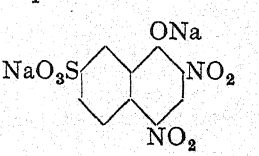
Isodibenzanthrone.

Classification of Dyestuffs

The simplest method of classifying dye-stuffs is to arrange them according to the manner in which they are applied to the material. Representatives of all the more important types of dyes have already been described in earlier pages of this book and their characteristics may now be summarised as follows.

Dye-stuffs may be subdivided into seven main groups, namely (1) acid dyes, (2) basic or tannin dyes, (3) direct or substantive dyes, (4) mordant dyes, (5) vat dyes, (6) developed or ingrain dyes, (7) sulphur dyes. In some cases a given dye may fall into two or more of these categories.

Acid Dyes.—These are chiefly the sodium salts of sulphonic acids and of nitrophenolic dyes. They are absorbed directly on wool from a bath which has been acidified with acetic or sulphuric acid. Dyes of this group have very little affinity for cotton even if used with mordants, and they do not yield lakes with tannin. An example of an acid dye is *naphthol yellow S.*



Naphthol yellow S.

Basic or Tannin Dyes are usually salts of colour bases with hydro-

chloric acid or zinc chloride, *e.g. magenta, rhodamine B, malachite green.* They are mainly employed for cotton with the aid of tannin mordant, although they can be readily attached directly to wool.

Direct or Substantive Cotton Dyes.—The discovery of direct cotton dyes was made by Böttiger in 1884. The majority of them are salts of azo-compounds derived from benzidine or similar bases. They are soluble in water and dye cotton and cellulose rayon directly from a bath containing sulphuric acid. Direct cotton dyes are in general not as brilliant as the basic dyes, nor as fast as mordant dyes. They are more liable to injury during the finishing processes and are also sensitive to impurities in the material. A typical dye of this group is *Congo Red.*

Mordant Dyes.—In this class are found a large number of dyes of widely differing chemical types ; most of them are acidic in nature and all form lakes with mordants. The methods of attaching them to the fibre vary considerably with the nature of the dye and of the material. The most important application of mordant dyes is to wool which has been mordanted with chromium, copper, iron or aluminium. Examples are *alizarin* and many of its derivatives. The chief use with cotton is in the preparation of *Turkey Red.*

Vat Dyes are insoluble in water, hence they cannot be employed directly for dyeing but must first be reduced to a soluble leuco-form. Reduction is commonly effected by means of alkali and sodium hyposulphite, $Na_2S_2O_4$, and owing to the strongly alkaline bath vat dyes are applied to cotton rather than to woollen goods. This disadvantage can be overcome by special methods (see indigosols and solubilised indanthrene). The leuco compounds are soluble in alkali and in this form are readily absorbed by the fibre. The treated material is then allowed to stand in air when the leuco compound is oxidised back to the original dye-stuff, which remains firmly embedded in the cloth. Very fast colours of almost any desired shade can be obtained in this group. Examples of vat dyes are *indigo, indanthrene* and various *anthraquinone derivatives.*

Developed Dyes, Ingrain Dyes. Under this heading are included all those dyes, the last stage in the production of which is carried out on the fibre itself. Mordant dyes are excepted and form a separate group. Three main types of developed dyes are recognised :

(a) *Ice colours,* which are generally used on cotton. They are prepared by impregnating the material with the secondary component of an azo-dye, *e.g.* alkaline β-naphthol ; the cloth is then dried and immersed in a cooled bath of a diazonium salt, *e.g. p*-nitrobenzene-diazonium chloride, $NO_2.C_6H_4.N_2Cl$. In this example the azo dye p-*Nitraniline Red* is produced. Various modifications of the process are in use, all of which give very fast ingrained colours.

(b) The material is first dyed with a direct cotton dye containing an amino group. The dye is then diazotised on the cloth and coupled (developed) with a secondary component to form an azo dye.

(c) *Aniline black* process. In this method aniline black is produced

either by (1) impregnating the cloth with aniline salt, followed by treatment with an oxidising agent, or (2) heating the cloth with a solution of aniline hydrochloride to which has been added either potassium bichromate and hydrochloric acid or potassium chlorate and a vanadium salt as catalyst.

Sulphur Dyes.—These are complex dyes containing sulphur, which are insoluble in water but soluble in aqueous sodium sulphide. They are prepared by heating various amino compounds, *e.g. p*-phenylene-diamine, with sodium sulphide and sulphur, thus yielding *sulphur blacks*. The sulphur dyes are applied to cotton by use of aqueous sodium sulphide as solvent, followed by oxidation in air or other suitable treatment.

XVI

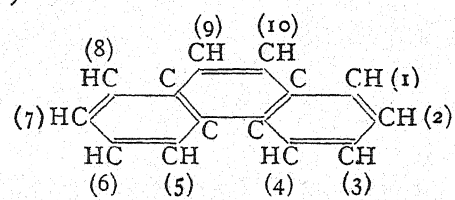
Phenanthrene Group

Phenanthrene, as already stated on p. 549, is found with its structural isomeride anthracene in the anthracene oil of coal tar. After purification of the crude anthracene by means of pyridine bases or solvent naphtha, the phenanthrene, owing to its greater solubility, remains in the mother liquors, from which it is isolated. The two hydrocarbons may also be separated by the use of carbon disulphide, or by partial oxidation, which results in anthracene being first attacked. In any case the production of phenanthrene is a matter of small technical importance, since all efforts to make use of it in the dye-stuff industry have so far been fruitless.

In the pure state phenanthrene forms white glistening plates, m.p. 99° and b.p. 340°. It dissolves very easily in ether and benzene, but less readily in alcohol, glacial acetic acid and carbon disulphide. The solutions exhibit a blue fluorescence.

Constitution and Synthesis of Phenanthrene

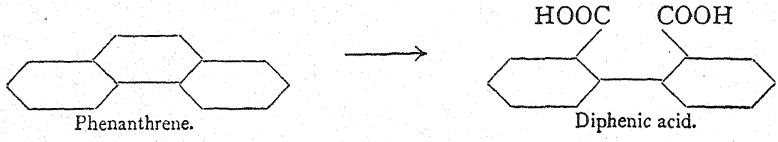
From its chemical behaviour and methods of synthesis, phenanthrene has been assigned the following constitution (Fittig and Ostermayer, Graebe and Glaser):



The positions occupied by substituents in phenanthrene derivatives are indicated by the use of numbers as shown above.

As will be seen from the formula, phenanthrene may be regarded either as a derivative of diphenyl or of naphthalene. Its connection with diphenyl is shown by a number of syntheses, as well as by its degradation to this hydrocarbon. For example, when phenanthrene is oxidised with

chromic acid it first yields phenanthraquinone (see p. 576) and then diphenic acid (p. 502), a derivative of diphenyl. Hence it must be derived

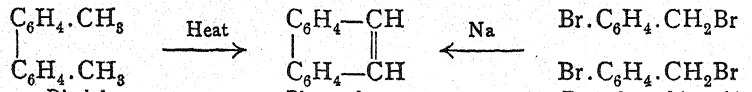


Phenanthrene. Diphenic acid.

from diphenyl, $C_6H_5.C_6H_5$, in such a way that the group C_2H_2 is attached to each benzene nucleus in an *o*-position to the bond linking the nuclei. The conversion of phenanthraquinone and its derivatives into derivatives of diphenyl-methane or fluorene, as described on p. 505, also supports this deduction. Further confirmation is obtained from syntheses.

Phenanthrene may be synthesised by the following methods :

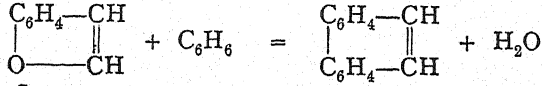
1. By various pyrogenic reactions, such as by leading stilbene, dibenzyl, toluene, *o*-ditolyl, or a mixture of diphenyl and ethylene through red-hot tubes.



o-Ditolyl. Phenanthrene. *o*-Bromobenzyl bromide.

2. By treating *o*-bromobenzyl bromide with sodium.

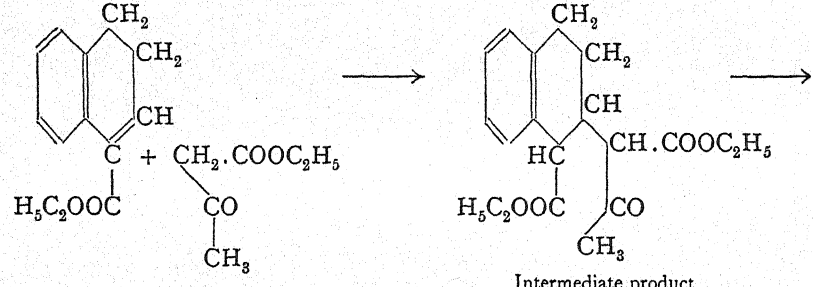
3. From coumarone by heating with benzene.



Coumarone.

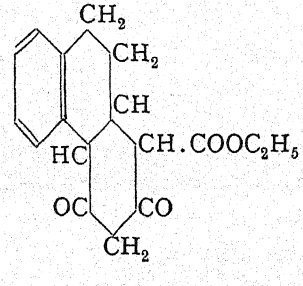
4. The relationship between phenanthrene and naphthalene is illustrated by the following synthesis from a derivative of naphthalene :

I.



Intermediate product

II.



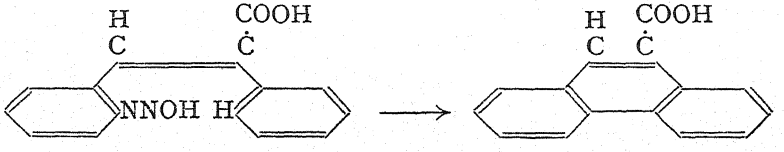
Dihydro-α-naphthoic ester (I) condenses with acetoacetic ester to give a diketo-octahydro-phenanthrene carboxylic ester (II), which on hydrolysis and elimination of carbon dioxide yields diketo-octahydro-phenanthrene. The latter on distillation with zinc dust is converted into phenanthrene.

5. A general method, developed by Pschorr [1] for preparing phenanthrene and its derivatives without employing high temperatures, is based on Perkin's reaction (p. 450).

o-Nitrobenzaldehyde may be condensed with acetic anhydride, in the presence of sodium phenylacetic acid, to form α-phenyl-*o*-nitrocinnamic acid.

$$NO_2.C_6H_4.CHO + HOOC.CH_2.C_6H_5 = NO_2.C_6H_4.CH:C\begin{matrix}COOH\\ \\ C_6H_5\end{matrix} + H_2O$$

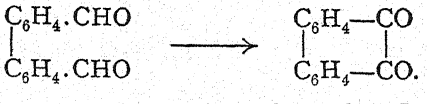
This may be reduced to the amino-compound, which when diazotised and shaken in sulphuric acid solution with copper powder, yields nitrogen, water and phenanthrene-10-carboxylic acid. The latter loses carbon dioxide on distillation and is converted into phenanthrene.



This procedure is adapted to the preparation of a large number of phenanthrene derivatives, since in place of nitrobenzaldehyde and phenylacetic acid we may also employ their substitution products. As will be seen shortly, the method has been used for the preparation of certain phenanthrene derivatives which are of special interest as being hydrolytic products of alkaloids. In addition, this synthesis has furnished valuable information regarding the constitution of a number of monosubstitution products of phenanthrene, such as sulphonic acids, amino- and nitro-compounds.

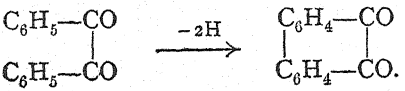
Windaus [2] has recently introduced a small modification of Pschorr's synthesis. Whereas Pschorr utilises the condensation product of *o*-nitroaldehydes and phenylacetic derivatives, Windaus employs the products obtained from the unsubstituted aldehydes and oxindole (p. 634). In the former case the nitrogen required for ring closure is present in the aromatic aldehyde; in the latter it is contained in the phenylacetic derivative (oxindole). Windaus was thus enabled to synthesise phenanthrene derivatives (*e.g.* 9-methyl-phenanthrene, m.p. 88° to 89°) which he had isolated as degradation products of the alkaloid colchicin.

6. Diphenyl-*o* : *o'*-dialdehyde, when warmed with an aqueous alcoholic solution of potassium cyanide, undergoes a form of benzoin condensation and is converted into phenanthraquinone.[3]



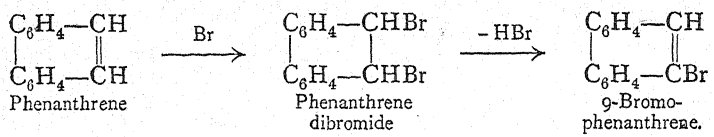
[1] R. Pschorr, *Ber.*, 1896, **29**, 496. [2] A. Windaus and co-workers, *Ber.*, 1924, **57**, 1871, 1875.
[3] F. Mayer, *Ber.*, 1912, **45**, 1102.

7. Benzil yields phenanthraquinone when melted with aluminium chloride. This synthesis may also be applied to derivatives of benzil.[1]



Chemical Behaviour of Phenanthrene.—In its chemical reactions phenanthrene is more closely related to diphenyl than to naphthalene. The central benzene ring, formed by linking up the diphenyl rings with the group CH : CH, is less stable than the other two. In other words, the (9:10) "bridge" of phenanthrene is attacked by reagents much more easily than the rest of the molecule and is also readily ruptured with the formation of diphenyl derivatives (see p. 568).

Two examples will illustrate the ease with which the bridge is attacked. Bromine reacts with phenanthrene [2] to give the 9 : 10-dibromide, and this on being warmed splits off hydrogen bromide and is transformed into 9-bromo-phenanthrene :



In the presence of platinum black, hydrogen unites with phenanthrene to form 9:10-dihydro-phenanthrene,[3] $C_{14}H_{12}$, a white crystalline mass of melting-point 94° to 95°.

Phenanthrene also possesses many points in common with its structural isomeride anthracene, from which it differs, however, not only in its greater solubility in the common solvents, but above all in the fact that it is less readily affected by oxidising agents.

Substitution Products of Phenanthrene

From the established formula of phenanthrene may be derived five different monosubstitution products, corresponding to the positions 1, 2, 3, 4, and 10 respectively.

It will readily be seen that the hydrogen atoms in the "bridge" are similarly situated, hence the 9- and 10-substitution products are the same.

A comparatively large number of disubstitution derivatives is theoretically possible, and with still further substitution the number of isomerides increases in a manner alarming to the experimenter.

This enormous increase in the possibilities of isomerism presents great difficulties in the way of preparing phenanthrene derivatives directly from the hydrocarbon according to methods usual in the aromatic series. In

[1] R. Scholl and Schwarzer, *Ber.*, 1922, 55, 324. [2] Addition occurs rapidly in the presence of peroxides, even in absence of light. Kharasch, White and Mayo, *J. Org. Chem.*, 1937, 2, 574.
[3] J. Schmidt and E. Fischer, *Ber.*, 1908, 41, 4225. See also *Ber.*, 1907, 40, 4240.

addition, the physical properties of many phenanthrene compounds are not favourable to experimental investigation.

For these reasons and more particularly owing to the fact that, contrary to expectation, it has not been possible to use these compounds on any considerable scale in the dyeing industry, chemists for decades back have hesitated to enter upon a systematic study of the phenanthrene group. Only in recent years have attempts been made from different quarters to supply the deficiency. An impetus towards this end was given by researches proving the existence of a close relationship between phenanthrene and certain important natural products such as plant alkaloids and the steroids (*q.v.*).

As the result of the work of a number of different investigators,[1] it has been established with certainty that *morphine*, *codeine* and *thebaine* contain a phenanthrene nucleus, and further that morphine and codeine are derived from a *tetrahydro-phenanthrene*, and thebaine from a *dihydro-phenanthrene*.

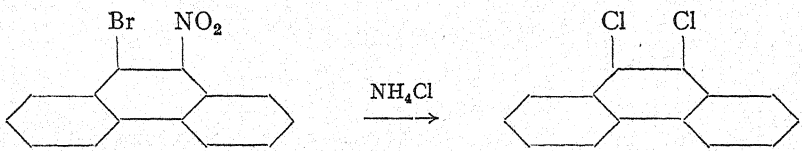
The Corydalis alkaloids and colchicin also contain the phenanthrene structure, and in certain sesquiterpenes a hydrogenated phenanthrene or anthracene nucleus may be present.[2]

Following the above discoveries a number of investigations were made with the object of preparing new derivatives of phenanthrene, either synthetically or directly from the hydrocarbon.[3]

Thus, for example, 3-*nitro-phenanthrene*, m.p. 170° to 171°, and 9-*nitro-phenanthrene*, m.p. 116° to 117°, have been prepared by direct nitration, and from these the corresponding *amino-phenanthrenes* have been obtained by reduction.

Nevertheless the preparation of nitro-phenanthrenes by direct nitration is tedious, owing to the resinification which so easily occurs. Halogen-substitution products of phenanthrene are less troublesome to nitrate, and when the 9-bromo-phenanthrene described on p. 570 is heated with nitric acid it yields 9-*bromo*-10-*nitro-phenanthrene*, m.p. 206°.

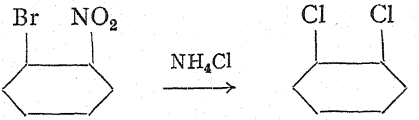
An observation of general interest has been made in connection with this compound.[4] When heated in a closed tube to 320° with ammonium chloride, it is converted comparatively smoothly into 9 : 10-*dichloro-phenanthrene*, m.p. 160° to 161°.



The reaction may also be applied to other aromatic compounds.

[1] Vongerichten, *Ber.*, 1901, **34**, 767, 1162, 2722. Knorr, *Ber.*, 1894, **27**, 1146. Freund, *Ber.*, 1899, **32**, 168. [2] F. W. Semmler, *Ber.*, 1907, **40**, 3521 ; also *J. C. S. Ann. Rep.*, 1924, p. 101. [3] A. Werner and co-workers, *Ann.*, 1902, **321**, 248 ; **322**, 135. J. Schmidt and co-workers, *Ber.*, Vols. **33-60**. H. Sandqvist, *Ann.*, 1913, **398**, 125 ; 1918, **417**, 1. [4] J. Schmidt and Ladner, *Ber.*, 1904, **37**, 4402. J. Schmidt and Wagner, *Ann.*, 1912, **387**, 164.

For example, *o*-bromo-nitrobenzene under the same conditions yields *o*-dichloro-benzene.



A condition for the success of this reaction is the *o*-position of the substituents, since *m*- and *p*-bromo-nitrobenzenes remain unchanged.

Sulphonation of phenanthrene leads to the production of 3-, 2- and 9-*phenanthrene sulphonic acids*, $C_{14}H_9.SO_3H$.

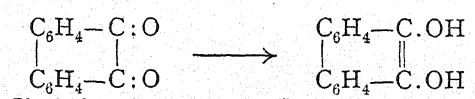
Hydroxy-phenanthrenes

Of more importance than the compounds just described are the **hydroxy-phenanthrenes**, certain of which, as will be seen later, have been obtained as degradation products of the opium alkaloids morphine, codeine and thebaine. They are therefore of interest in connection with the constitution of these substances. Hydroxy-phenanthrenes may be prepared from the sulphonic acids by fusion with potash, from the amino-derivatives by way of the diazo-reaction, or by the synthetic method of Pschorr (p. 569).

All of the five possible **monohydroxy-phenanthrenes** are known, either in the free state or as the methyl ethers.

1-*Hydroxy-phenanthrene*,[1]	melting-point	156°;	*Methyl ether*,	melting-point	106°.
2-*Hydroxy-phenanthrene*,	,,	168°;	,,	,,	99°.
3-*Hydroxy-phenanthrene*,	,,	124°;	,,	,,	63°.
4-*Hydroxy-phenanthrene*,	,,	106° to 109°;	,,	,,	68°.
9-*Hydroxy-phenanthrene*,	,,	153°.			

Among the **dihydroxy-derivatives** the most accessible is 9 : 10-*dihydroxy-phenanthrene* or hydro-phenanthraquinone, m.p. 147° to 148°. It is conveniently prepared by reducing phenanthraquinone with hydrogen sulphide, or with the calculated amount (1 mol.) of phenylhydrazine in alcoholic solution.



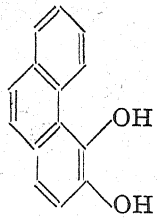
Phenanthraquinone — Hydro-phenanthraquinone.

In a similar manner the nitro-derivatives of phenanthraquinone may be converted into the corresponding hydro-phenanthraquinones.[2]

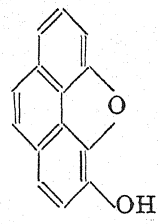
The compounds *morphol* and *morphenol* are important degradation products of morphine and its methyl ether codeine.

Morphol is a disruption product of morphine in which no nitrogen is present. It was prepared from morphine methiodide by heating with acetic anhydride, and for long could only be identified generally as a

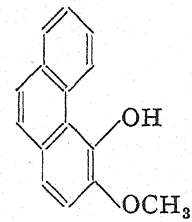
[1] J. B. Shoesmith and Guthrie, *J. C. S.*, 1928, 2332. [2] J. Schmidt and Kämpf, *Ber.*, 1902, 35, 3123.



Morphol, 3 : 4-dihydroxy-phenanthrene, m.p. 143°



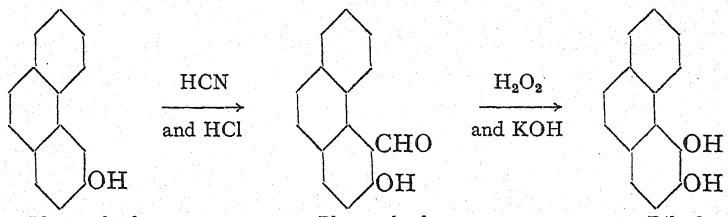
Morphenol, m.p. 135°



Methyl-morphol, 3-methoxy-4-hydroxy-phenanthrene.

dihydroxy-phenanthrene. Subsequently, some information as to the position of the hydroxyl groups was obtained from the observation that the dihydroxy-phenanthraquinone prepared from morphol possessed dyeing properties [1] similar to those of alizarin, and hence should contain the hydroxyl groups in the ortho-position (see p. 555). After the relationship between morphol and morphenol had been made clear by reducing the latter to the former, the structure of 3:4-dihydroxy-phenanthrene [1] was proposed for morphol. Confirmation of this formula was supplied by the synthesis of dimethyl-morphol described below, and later by Barger's synthesis of morphol itself.

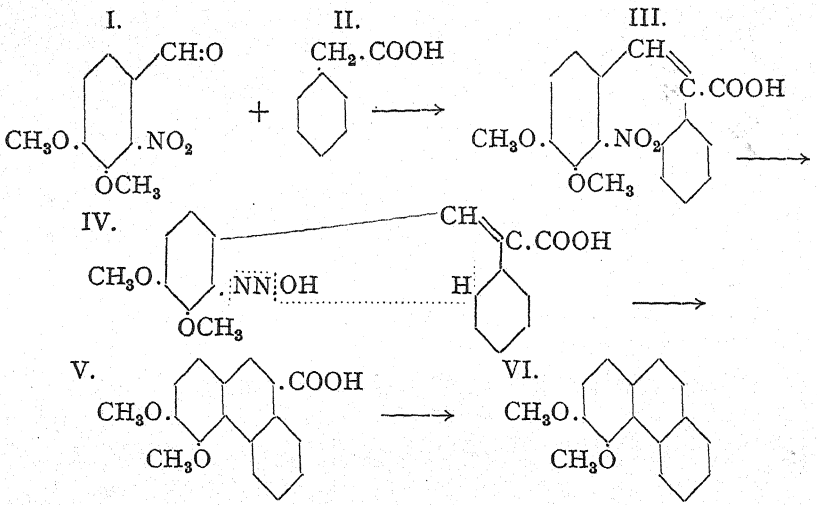
Synthesis of Morphol.[2]—This was effected from 3-phenanthrol-4-aldehyde (obtained by the interaction of 3-phenanthrol, hydrogen cyanide and hydrogen chloride in the presence of aluminium chloride) by treating it with hydrogen peroxide and potassium hydroxide in aqueous pyridine solution.[3] The morphol or 3:4-dihydroxy-phenanthrene obtained melted at 142°.



3-Phenanthrol — 3-Phenanthrol-4-aldehyde — 3 : 4-Dihydroxy-phenanthrene.

Synthesis of Dimethyl-morphol.[4]—The starting-point of this synthesis was the methyl ether of vicinal *o*-nitrovanillin (I), which was condensed with the sodium salt of phenylacetic acid (II) by Perkin's reaction to give α-phenyl-2-nitro-3:4-dimethoxy-cinnamic acid (III). The diazo-compound (IV) of the corresponding amino-acid in sulphuric acid solution parted with nitrogen and water with the formation of 3 : 4-dimethoxy-phenanthrene-9-carboxylic acid (V), which on distillation gave carbon dioxide and dimethoxy-phenanthrene (VI).

[1] Vongerichten, *Ber.*, 1900, **33**, 352. [2] G. Barger, *J. C. S.*, 1918, **113**, 218. [3] This reaction has been shown by H. D. Dakin (*Am. Ch. J.*, 1909, **42**, 477) to be a general method of converting hydroxy derivatives of benzaldehyde and acetophenone into polyhydric phenols. [4] Pschorr and Simuleanu, *Ber.*, 1900, **33**, 1811.

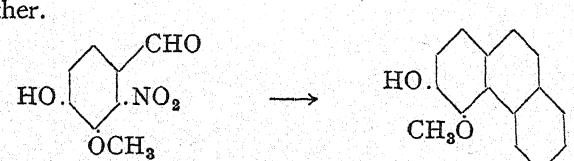


This synthesis establishes the 3:4-positions of the two methoxyl groups, as it is improbable that any intramolecular rearrangement could take place under the above conditions of experiment.

Dimethyl-morphol (formula VI) crystallises from alcohol in colourless leaflets, m.p. 44°. With picric acid it yields a double compound, m.p. 105° to 106°, crystallising in ruby red prisms.

The synthetic 3:4-dimethoxy-phenanthrene is identical with the dimethyl-morphol prepared from methyl-morphol, a degradation product of codeine.[1]

In connection with the constitution of morphine, the molecule of which contains an alcoholic hydroxyl and a phenolic group,[2] it was of importance to decide which of the hydroxyls of morphol corresponds to the phenolic hydroxyl. Now codeine, a methyl ether of morphine in which the methoxy group takes the place of the phenolic hydroxyl of the latter compound, had been degraded to acetyl-methyl-morphol. All that was necessary, therefore, was to determine the position of the methoxy group in this acetyl derivative. The point was settled by Pschorr's synthesis of the acetyl derivative of 3-hydroxy-4-methoxy-phenanthrene by the above method, using vicinal *o*-nitrovanillin in place of the corresponding ether.



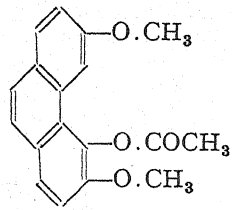
The synthetic 3-*hydroxy*-4-*methoxy*-*phenanthrene* prepared in this manner differs considerably from the methyl-morphol obtained as a disruption product of α-methyl-morphimethine from codeine; hence it

[1] Vongerichten, *Ber.*, 1900, **33**, 1824. [2] Matthiessen and Wright, *Proc. Roy. Soc.*, 1869, **17**, 364. Hesse, *Ann.*, 1884, **222**, 203.

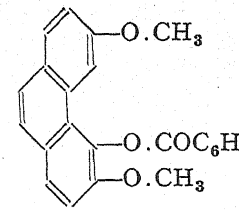
was concluded that the latter is represented by the structure 3-methoxy-4-hydroxy-phenanthrene. This inference was shortly afterwards confirmed by the synthesis of 3-methoxy-4-acetoxy-phenanthraquinone,[1] which was found to be identical with the acetyl-methyl-morphol-quinone from morphine.

Morphenol (p. 573), which represents the molecular skeleton of morphine and thebaine, yields on fusion with alkali 3 : 4 : 5-trihydroxy-phenanthrene,[2] m.p. 148°.

The following two hydroxy derivatives of phenanthrene have been obtained from the opium alkaloid thebaine under different experimental conditions.

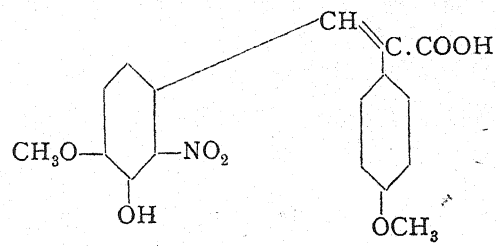


Acetyl-thebaol
(3 : 6-dimethoxy-4-acetoxy-phenanthrene)



Benzoyl-thebaol.

Acetyl-thebaol, m.p. 118° to 122°, has been prepared from thebaine by heating it with acetic anhydride (Freund). When treated with sodium ethoxide it is converted into **thebaol, 3:6-dimethoxy-4-hydroxy-phenanthrene**, m.p. 94°. The constitution of thebaol was proved by Pschorr, who synthesised it from vicinal *o*-nitro-isovanillin and *p*-methoxy-phenyl-acetic acid by the method previously described for the hydroxy phenanthrenes.[3] The first step in the process is the formation of the compound indicated above.



This synthesis also establishes the position of the two methoxy-groups of thebaine, a point which will be referred to later. *Benzoyl-thebaol* has been prepared in the form of colourless needles, m.p. 169°, by the action of benzoyl chloride on thebaine [4] at 0°.

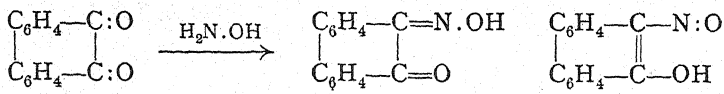
3:4:6:8-Tetramethoxy-phenanthrene, m.p. 108°, has been obtained by the degradation of the alkaloid morphothebaine. It was also synthesised by Pschorr [5] by the method already quoted.

[1] Pschorr and Vogtherr, *Ber.*, 1902, **35**, 4412. [2] Vongerichten and Dittmer, *Ber.*, 1906, **39**, 1718. For a synthesis of 3 : 4 ·5-*trimethoxy-phenanthrene* see R. Pschorr, *Ann.*, 1912, **391**, 40. [3] Pschorr, Seydel and Stöhrer, *Ber.*, 1902, **35**, 4400. [4] Pschorr and Haas, *Ber.*, 1906, **39**, 16. [5] Pschorr and Knöffler, *Ann.*, 1911, **382**, 50.

Phenanthraquinone and its Derivatives

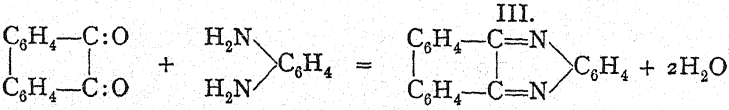
Phenanthraquinone, $C_{14}H_8O_2$ (formula I below), is generally prepared by oxidising phenanthrene with chromic acid in glacial acetic acid solution. It crystallises in orange-coloured needles, m.p. 208°. At ordinary temperatures it is readily soluble in benzene but dissolves less readily in ether, alcohol and glacial acetic acid. It is odourless and not volatile with steam. When a solution of phenanthraquinone in glacial acetic acid is treated with sulphuric acid and toluene containing thiotolene (see p. 626), a blue-green coloration is developed; after dilution with water and extraction with ether the colour changes to violet (*Laubenheimer's reaction*). As already indicated under β-naphthaquinone, it is closely related to the *a*-diketones in its properties. With hydroxylamine it forms, according to conditions, a monoxime (m.p. 160°) or a dioxime. The former exhibits tautomerism, reacting according to either of the formulæ II*a*, or II*b*.

I. II*a*. II*b*.



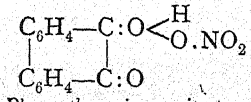
Phenanthraquinone, like other *a*-diketones, reacts with *o*-diamines to give phenazine derivatives. Thus with *o*-phenylene diamine it condenses to form *phenanthraphenazine* (III):

III.

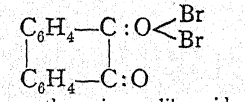


The conversion of phenanthraquinone into diphenic acid by oxidation with chromic acid mixture, and the formation of diphenylene glycollic acid by heating it with aqueous potassium hydroxide, have already been mentioned (see pp. 502 and 505). With *alcoholic* potash phenanthraquinone reacts to give diphenic acid or more complex products.[1]

On treatment with nitric acid (sp. gr. 1·4) at moderate temperatures phenanthraquinone yields a *mono-nitrate*, and with excess of bromine at low temperatures a dibromo addition product. Considering the ease with which these compounds lose nitric acid and bromine respectively, it is probable that they are *oxonium compounds* (see Pyrone) of the following structure:



Phenanthraquinone nitrate.



Phenanthraquinone dibromide.

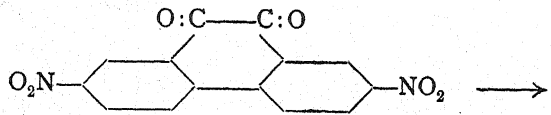
[1] R. Meyer and Spengler, *Ber.*, 1905, **38**, 440, 950.

Nitro-derivatives of Phenanthraquinone

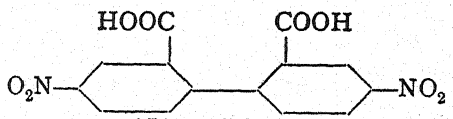
All the possible mononitro derivatives are known, with the exception of 1-nitro-phenanthraquinone. Of the dinitro-compounds the symmetrical 2 : 7- and 4 : 5-*dinitro-phenanthraquinones* have been prepared.

3-*Nitro-phenanthraquinone* has been obtained by Schmidt and Kämpf, and its structure confirmed by the oxidation of 3-nitro-phenanthrene.[1] The remaining nitro-compounds have been prepared by direct nitration of phenanthraquinone. When boiled for two to three minutes with concentrated nitric acid of sp. gr. 1·45 the quinone is converted mainly into a mixture of 2- and 4-*nitro-phenanthraquinones*.[2] Energetic nitration yields exclusively the above symmetrical dinitro-derivatives.

There is a tendency for the two symmetrical dinitro-derivatives to be formed by the nitration of any of the mononitro-compounds so far known. The pronounced tendency for substituents to assume the 2 : 7-positions is also apparent in other substitution reactions.



2:7-Dinitro-phenanthraquinone



pp'-Dinitro-diphenic acid.

On oxidation with potassium bichromate and sulphuric acid all nitro-derivatives of phenanthraquinone yield the corresponding nitro-diphenic acids.

In the following table will be found the melting-points of all known nitro-derivatives of phenanthraquinone, together with those of the corresponding diphenic acids.

Name.	Melting-point.	Name.	Melting-point.
2-Nitro-phenanthraquinone .	257-258°	*p*-Nitro-diphenic acid[3] .	220-221°
3-Nitro-phenanthraquinone .	279-280° (decomp.)	*m*-Nitro-diphenic acid .	268°
4-Nitro-phenanthraquinone .	179-180°	*o*-Nitro-diphenic acid .	248-250° (decomp.)
2 : 7-Dinitro-phenanthraquinone	301-303°	*pp'*-Dinitro-diphenic acid[4] .	253°
4 : 5-Dinitro-phenanthraquinone	228°	*oo'*-Dinitro-diphenic acid .	303° (decomp.)

[1] J. Schmidt and co-workers, *Ber.*, 1902, **35**, 3117; 1908, **41**, 3679; 1901, **34**, 3531. [2] J. Schmidt and Austin, *Ber.*, 1903, **36**, 3730. Schmidt and Kämpf, *Ber.*, **36**, 3734. [3] F. J. Moore and C. H. Huntress, *J. A. C. S.*, 1927, **49**, 1324. [4] The compound of melting-point 253° contains 1 mol. H_2O.

On reduction with tin and hydrochloric acid the nitro-compounds yield the corresponding *amino-hydro-phenanthraquinones*, which are generally very unstable in the free state and readily undergo oxidation to *amino-quinones*. The latter can be diazotised and converted in the usual manner into various substitution products of phenanthraquinone.

It will thus be seen that the nitro-phenanthraquinones provide the key to the constitution of most of the other substitution products of phenanthraquinone.

They have, for example, been of service in determining the constitution of the *bromo-derivatives*.[1] These can be obtained partly by direct bromination, and partly by the oxidation of bromo-phenanthrenes. On oxidation they yield the corresponding bromo-diphenic acids, as summarised in the following table :

Name.	Melting-point.	Name.	Melting-point.
2-Bromo-phenanthraquinone . .	233-234°	*p*-Bromo-diphenic acid .	238-239°
3-Bromo-phenanthraquinone . .	268°	*m*-Bromo-diphenic acid .	257° (decomp.)
4-Bromo-phenanthraquinone . .	126°	—	—
2 : 7-Dibromo-phenanthraquinone .	323°	*pp'*-Dibromo-diphenic acid	277-278°

Hydroxy derivatives of phenanthraquinone may be prepared as indicated above from the amino-compounds, or by the oxidation of acylated hydroxy-phenanthrenes. Some of these have been of value in identifying the hydroxy-phenanthrenes described earlier, which were obtained by the degradation of morphine, codeine and thebaine.

2-*Hydroxy-phenanthraquinone*, violet black needles, m.p. 280° to 283°.

3-*Hydroxy-phenanthraquinone*, needles resembling alizarin ; acetyl derivative, m.p. 199° to 201°.

4-*Hydroxy-phenanthraquinone*, dark red needles ; acetyl derivative, m.p. 188° to 189°.

4 : 5-*Dihydroxy-phenanthraquinone*, chars above 400°, dimethyl ether, m.p. 190° to 191°.

2 : 7-*Dihydroxy-phenanthraquinone*, decomposes above 400° ; diacetyl derivative, m.p. 236°.

3 : 4-*Dihydroxy-phenanthraquinone*, **morphol-quinone**, red ; diacetyl derivative, m.p. 196°. Has been obtained synthetically, as already indicated, and also from phenanthrene by way of 3-nitro-phenanthraquinone.

3-*Methoxy*-4-*acetoxy-phenanthraquinone*, **acetyl-methyl-morphol-quinone**, m.p. 205° to 206°.

3 : 6-*Dimethoxy*-4-*acetoxy-phenanthraquinone*, **acetyl-thebaol-quinone**, m.p. 203°.

2 : 3 : 4-*Trihydroxy-phenanthraquinone*, m.p. 185° with decomposition.

[1] J. Schmidt, *Ber.*, 1904, **37**, 3551.

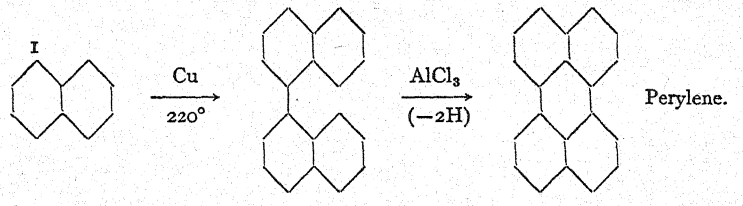
XVII

Other Hydrocarbons containing Condensed Nuclei

In addition to naphthalene, anthracene and phenanthrene, a number of hydrocarbons of still higher molecular weight are known containing condensed benzene rings, many of which occur in the fraction of coal tar boiling above 360°. These may be described very briefly.[1]

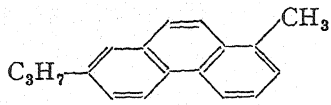
Retene is present in certain fossil coniferous resins found in deposits of peat and brown coal. It is formed by the dry distillation of the wood of conifers, and can therefore be obtained from pine tar. Part of the retene in these sources probably originates from the diterpene derivative **abietic acid** (m.p. 153°), which has been isolated from resin or colophonium (p. 481) and yields retene on being heated with sulphur.[2] **Fichtelite**, $C_{19}H_{34}$, a completely saturated higher homologue of perhydroretene, is also found in fossil coniferous resins.[3] Phenanthrene, **pyrene** and **fluoranthene** also occur in "Stupp" fat, a by-product obtained from the treatment of mercury ores in Idria.

In recent years a number of hydrocarbons of this type have been prepared synthetically.[4] Scholl has shown that the condensation of aromatic nuclei with loss of hydrogen—a process long known in the form of pyrogenic reactions—is greatly accelerated in the presence of aluminium chloride. In this way condensation can be satisfactorily effected at as low a temperature as 100°, and the method can therefore be applied to substances which could not survive the drastic conditions of a pyrogenic reaction. The practical details have been worked out particularly for the union of aromatic nuclei in cases where elimination of hydrogen leads to the formation of new rings. Thus α-iodonaphthalene has been converted into 1 : 1′-dinaphthyl, and the latter by heating with aluminium chloride (*dry bake*) gave **perylene**, $C_{20}H_{12}$, which was obtained in the form of yellow or bronze leaflets of m.p. 264° to 265°.

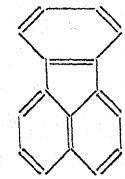


[1] See also *The Higher Coal Tar Hydrocarbons*, by A. E. Everest (Longmans, Green, 1927). *Chemistry of Natural Products related to Phenanthrene*, L. F. Fieser (New York, 1937). Kon, *Ann. Rep.*, 1932, 163. [2] Veresterberg, *Ber.*, 1903, **36**, 4200. L. Ruzicka and M. Pfeiffer, *Helv. Chim. Acta*, 1925, **8**, 635. P. Levy, *Ber.*, 1926, **59**, 1302. [3] Ruzicka and Waldmann, *Helv.*, 1935, **18**, 611. [4] Scholl and co-workers, *Ann.*, 1912, **394**, 11; 1913, **398**, 82; *Ber.*, 1922, **54**, 109.

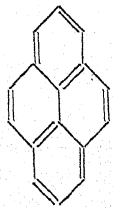
The formulæ for some of the better known compounds of this type are given below.



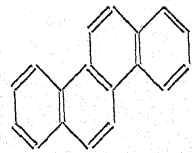
Retene, methyl-isopropyl-phenanthrene, m.p. 98°



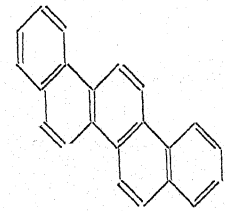
Fluoranthene, 1 : 2-benzacenaphthene, m.p. 110°.



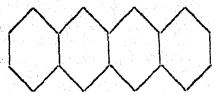
Pyrene, $C_{16}H_{10}$ m.p. 148°



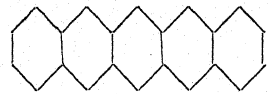
Chrysene, $C_{18}H_{12}$ m.p. 250°



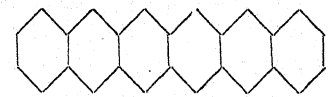
Picene, $C_{22}H_{14}$ m.p. 364°.



Naphthacene $C_{18}H_{12}$ (Red)



Pentacene $C_{22}H_{14}$ (Dark blue)



Hexacene. $C_{26}H_{16}$ (Green).

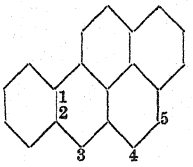
According to the manner in which the benzene nuclei are fused together there may be formed molecules of a linear type such as pentacene or angular ones such as chrysene or picene. Isomeric compounds of these two types differ markedly in their properties. Thus 1 : 2 : 5 : 6-dibenzanthracene (see p. 581) is colourless, whereas pentacene is dark blue. The reactivity of the meso positions in anthracene towards oxidising and reducing agents is diminished by the fusion of other benzene nuclei at the angular positions, but is increased when these are attached so as to form linear compounds.

Carcinogenic Compounds

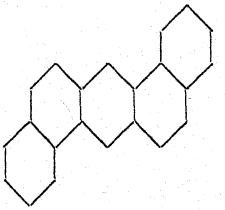
It is well known that continued contact with certain tars may lead to the development of cancer, but only within the last few years has information become available regarding the nature of the compounds which may give rise to the disease. Progress in this field is largely due to the work of Cook, who showed that **1 : 2-benzpyrene,**[1] a complex aromatic hydrocarbon present in tar, possesses very strong carcinogenic properties. Another hydrocarbon of similar nature which has been synthesised by Cook is **1 : 2 : 5 : 6-dibenzanthracene.** Various other compounds of this kind have been prepared, the molecules of which all contain the condensed ring system of phenanthrene. The physiological

[1] J. W. Cook, C. L. Hewett and I. Hieger, *Nature*, 1932, **130**, 926; *J. C. S.*, 1933, 395.

effect is, however, strongly dependent upon the molecular structure. Thus 4 : 5-benzpyrene and 1 : 2-benzanthracene are almost entirely inactive.



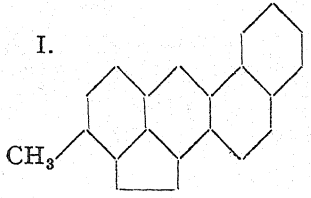
1 : 2-Benzpyrene



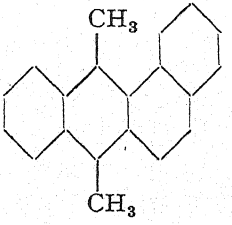
1 : 2 : 5 : 6-Dibenzanthracene.

The most potent carcinogenic compounds so far discovered are **methyl cholanthrene,** I, which is a simple transformation product of the deoxycholic acid of bile (see p. 587), and 9 : 10-dimethyl-1 : 2-benzanthracene, II. It has been suggested by Cook [1] that just as the sex hormones (p. 592) appear to result in the animal organism by the degradation of the sterols and bile acids, so the dehydrogenation of these compounds by a faulty mechanism may yield products of a carcinogenic nature.

I.



II.



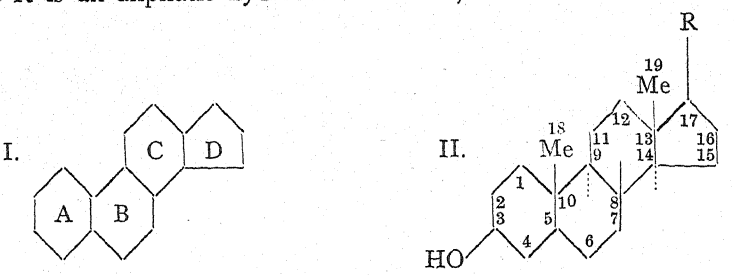
XVIII

Steroids [2]

Under the heading of steroids are included several important groups of natural products such as the sterols, bile acids, sex hormones, cardiac poisons and saponins. These compounds, believed to be related to the polyterpenes, are derived from a *hydrogenated* 1 : 2-*cyclopenteno-phenanthrene* (I) containing a fused structure of one 5-membered and three 6-membered rings. The majority of the steroids conform to the generalised formula II [3] and have a hydroxyl group in position 3, although in some this group is missing and others are ketonic or polyhydroxy in type. They vary considerably in the degree of hydrogenation of the rings and

[1] Cook, *Proc. Roy. Soc.*, 1933, **113B**, 273. [2] For general references see S. A. R. Kon, *Ann. Rep. Chem. Soc.*, 1933, 198; 1934, 207; J. W. Cook, *ibid.*, 1936, 341; R. K. Callow, *ibid.*, 1938, 281; H. D. Springall, *ibid.*, 1939, 286; F. S. Spring, *ibid.*, 1940, 332. Also L. F. Fieser, *The Chemistry of Natural Products related to Phenanthrene*, 2nd ed., New York, 1937; H. Sobotka, *Chem. Rev.*, 1934, 15, 311. [3] Unless otherwise indicated the rings in these formulæ are understood to be saturated. Nuclear hydrogen atoms are omitted for the sake of clearness.

in the nature of the residue R attached to position 17. In the typical **sterols** R is an aliphatic hydrocarbon chain; in the **bile acids** it is an



aliphatic carboxylic acid group; in the **sex hormones** it may become simplified to a hydroxyl group or ketonic oxygen. In the **cardiac poisons** and **saponins**, which are glycosides of hydroxy compounds, R is a heterocyclic structure containing oxygen in the ring.

Theoretically, the cyclic nucleus of four rings present in the steroids may exist in a number of isomeric forms, since the component rings (if hydrogenated) may be joined together by either *cis* or *trans* linkages as in the *cis* and *trans* decalins (p. 546). A further complexity arises from the *cis* or *trans* arrangement of a substituent attached to a saturated part of a ring, *e.g.* OH in position 3. As yet no satisfactory nomenclature has been devised capable of expressing clearly these steric arrangements. The *cis* or *trans* configuration of hydroxyl in position 3, for example, was originally stated relative to the neighbouring H atom linked to carbon atom 5. But in some of the sterols this hydrogen is missing owing to the presence of a double bond at 5 : 6 or 4 : 5. The arrangement of the OH group was then referred to the methyl group at position 10, a practice which led to confusion because in certain compounds the H and CH_3 attached to 5 and 10 respectively are situated in the *trans* position to one another, whereas in others they occupy the *cis* position. One and the same arrangement of the hydroxyl group was therefore described as *cis* or *trans* according to the standard of reference employed.

In the present stage of the development of these compounds the problem of nomenclature is somewhat simplified by the fact that rings B and C, and also C and D (formula I) appear in nearly all cases to be fused together by *trans* linkages in the natural steroids. Attention has therefore been concentrated mainly on expressing the steric arrangement of A and B, and of the substituent in position 3. Further reference to this point is made under cholesterol.

STEROLS

Sterols are complex alcohols found in many animal and vegetable oils and fats, partly in the free state and partly in the form of esters. From these sources they are isolated by hydrolysis with alcoholic potassium hydroxide, followed by extraction with ether or light petroleum. Sterols are extensively distributed in nature and may be regarded as fundamental

constituents of all living cells except those of bacteria. Among the chief members of the group are **cholesterol** and **ergosterol**, the former being found exclusively in animal organisms and the latter in this source and also in plants. Various other sterols such as **sitosterol** and **stigmasterol** occur only in plants and are described collectively as *phytosterols*. Some of the best known sterols are listed in the following table.

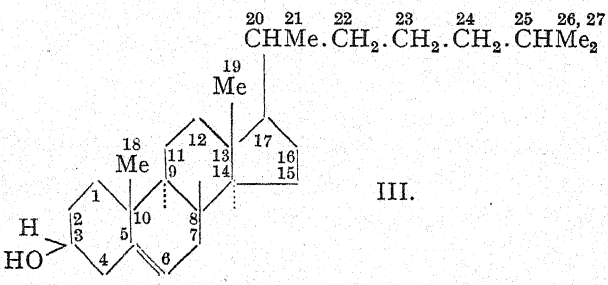
Sterols

		Double Bonds.	m.p.	$[\alpha]_D$*	Occurrence.
Cholesterol . . .	$C_{27}H_{45}OH$	1	148·5°	−37·5	All animal cells, gallstones, whale oil, etc.
Dihydrocholesterol .	$C_{27}H_{47}OH$	0	142°	+29·7	Found with cholesterol.
Coprosterol . .	$C_{27}H_{47}OH$	0	102°	+24·7	In fæces.
Zymosterol . . .	$C_{27}H_{43}OH$	2	109°	+50	Yeast.
Ergosterol . . .	$C_{28}H_{43}OH$	3	160°	−135	Ergot, yeast.
Ostreaosterol . .	$C_{29}H_{47}OH$	2	143°	−44	Oysters.
Fucosterol . . .	$C_{29}H_{47}OH$	2	124°	−38	Algæ.
Stigmasterol . .	$C_{29}H_{47}OH$	2	170°	−45	Calabar and soya beans.
γ-Sitosterol. . .	$C_{29}H_{49}OH$	1	137°	−33	Wheat.
Cinchol . . .	$C_{29}H_{49}OH$	1	140°	−34	Cinchona bark.

* The majority of these rotations are determined in chloroform solution. See Callow and Young, *Proc. Roy. Soc.*, 1936, A, **157**, 194.

Cholesterol, $C_{27}H_{45}OH$, is an unsaturated secondary alcohol which is widely distributed in the human organism, especially in the brain and nerves. It was first discovered in gallstones, from which it may be prepared. In these sources it is accompanied by the saturated compound, **dihydrocholesterol**, $C_{27}H_{47}OH$, m.p. 142°. Cholesterol is apparently synthesised in the animal organism, as sterols introduced in the form of food are largely eliminated unchanged. Cholesterol melts at 148·5° and is lævorotatory ($[\alpha]_D$ −37·5° in chloroform). It is insoluble in water, sparingly soluble in light petroleum, alcohol or acetone, and dissolves readily in carbon disulphide, benzene or ether. When a solution of the compound in chloroform is treated with sulphuric acid and acetic anhydride a blue coloration results (*Liebermann-Burchard*).

The structure of cholesterol has been established in connection with

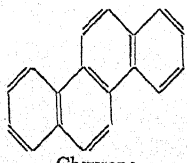


III.

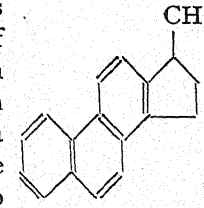
that of the closely related bile acids, and is believed to be represented by formula III (Me = CH_3), the rings being fully saturated except for a

double bond at 5 : 6. The presence of a secondary alcoholic grouping was early established by the formation of a mono-acetate and by the production of a ketone, **cholestenone** (fig. III with CO in place of CHOH and the double bond displaced to 4 : 5) when cholesterol is oxidised with copper oxide at 300°. The double bond is proved by the addition of two atoms of bromine and also by hydrogenation in the presence of platinum black to form the saturated alcohol **cholestanol** (*dihydrocholesterol*).[1] Further reduction of cholestenone or of cholesterol results in the loss of oxygen and addition of hydrogen to the double bond to give the saturated hydrocarbon **cholestane**, $C_{27}H_{48}$. The nature of the side chain at position 17 was demonstrated by Wieland's oxidation of cholesteryl acetate with chromic oxide, when disruption occurred with the formation of a volatile ketone, *2-methyl-heptanone-6*, $CH_3.CO.CH_2.CH_2.CH_2.CH(CH_3)_2$, which was isolated by steam distillation. This leads to the structure of the side chain as given in III.

Much of the earlier information on the constitution of the cyclic nucleus present in the sterols and bile acids was gained from the work of Windaus [2] and of Wieland. The results, especially when the formula for the saturated compound cholestane is taken into account, led to the belief that the nucleus contained a fusion of four rings, although the actual arrangement has only become known within the last few years. In 1927 Diels [3] dehydrogenated cholesterol with hot palladium charcoal and obtained chrysene $C_{18}H_{16}$. By treating cholesteryl chloride with selenium under milder conditions he isolated chrysene and a hydrocarbon $C_{25}H_{24}$ (generally known as **Diels' hydrocarbon**). Formulæ based upon hydrochrysene and other variations including five-membered rings proved unsatisfactory until the above-mentioned 1 : 2-cyclopenteno-hydrophenanthrene structure was advanced in 1932 by Rosenheim and King [4] and independently about the same time by Wieland.[5] In the following year Ruzicka [6] repeated the dehydrogenation of cholesterol with selenium and obtained no chrysene but only the hydrocarbon $C_{25}H_{24}$. Moreover, from ergosterol, $C_{28}H_{43}OH$, he isolated a hydrocarbon $C_{26}H_{26}$, which was thus a higher homologue of the Diels' hydrocarbon. Final confirmation of the Rosenheim-Wieland structure was given by the synthesis by Kon and co-workers [7] of 3-methyl-1 : 2-cyclopenteno-phenanthrene (I), which was proved to be identical with the Diels' hydrocarbon by an examination of derivatives, absorption spectra and crystal spacings. It is therefore clear that the selenium dehydrogenation of cholesterol leads to the elimination of methyl groups at 10 and 13 (necessary for the



Chrysene



I.

[1] Willstätter and E. Meyer, *Ber.*, 1908, 41, 2199. [2] *Z. physiol. Chem.*, 1932, 213, 147. [3] *Ann.*, 1927, 459, 1; *Ber.*, 1935, 68, 267. [4] *Nature*, 1932, 130, 315. [5] *Z. physiol. Chem.*, 1932, 210, 268. [6] *Helv.*, 1933, 16, 216, 812. [7] G. A. R. Kon, S. H. Harper and F. C. J. Ruzicka, *J. C. S.*, 1934, 124.

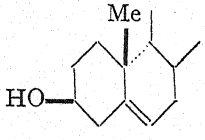
formation of the aromatic system) and to the replacement of the long side chain at position 17 by a methyl group; under more vigorous conditions a catalytic enlargement of the five-membered ring also occurs by absorption of the methyl group, which is then followed by dehydrogenation to form chrysene.

An important conclusion drawn from an X-ray examination of cholesterol and other steroids by Bernal [1] is that the molecule has a flat structure. Ruzicka pointed out that this can only occur if rings B and C are joined by *trans* linkages. From degradation experiments it is also concluded that C and D are fused together in the same manner. Further details regarding rings A and B are given below.

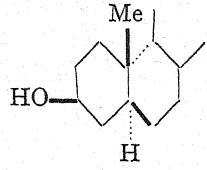
The attachment of hydroxyl to position 3 was established in connection with the work on bile acids described on p. 590.

Coprosterol, $C_{27}H_{47}OH$, is a saturated dextrorotatory stereoisomeride of cholestanol. It melts at 102° and has $[\alpha]_D$ +24·7° in chloroform solution. Coprosterol is formed in the intestines by bacterial hydrogenation of cholesterol and is therefore present in fæces. On vigorous reduction the hydroxyl group is replaced by hydrogen to give the saturated hydrocarbon **coprostane**, $C_{27}H_{48}$.

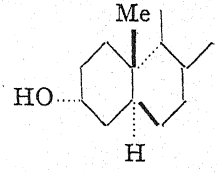
Relationship between Cholesterol and Coprosterol.—The stereochemical relationships between cholesterol, cholestanol (dihydrocholesterol), coprosterol and their epimerides have been examined by Windaus [2] and more particularly by Ruzicka.[3] They are probably represented by the following formulæ [4] in which only rings A and B are shown, the rest of the molecule being as in formula III, p. 583, with rings B and C, and also C and D, joined by *trans* linkages.



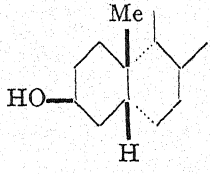
Cholesterol



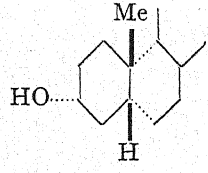
Cholestanol



epi-Cholestanol



Coprosterol



epi-Coprosterol.

It will be noted that the cholestane series is distinguished by a *trans* fusion of rings A and B, whereas in the coprostane series the fusion is by *cis* linkages. When the double bond in cholesterol is hydrogenated the H atom which becomes attached to position 5 may according to

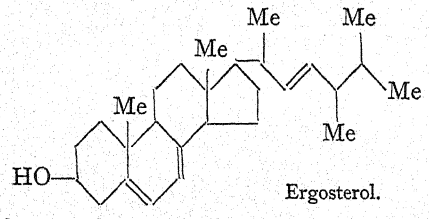
[1] *Chem. and Ind.*, 1932, 51, 466. [2] Windaus, *Ann.*, 1926, 447, 333. [3] L. Ruzicka and co-workers, *Helv.*, 1934, 17, 1407. [4] The *cis* and *trans* configurations are here indicated according to the method of Miescher and Fischer, *Chem. and Ind.*, 1939, 113.

experimental conditions assume either a *cis* or a *trans* configuration with respect to the methyl group at position 10, to form either coprosterol or cholestanol. In the presence of platinum black the latter compound is produced. Another isomeride of cholesterol is *allo*-**cholesterol,** prepared (together with *epiallo*-cholesterol) by reducing cholestenone with aluminium isopropoxide. Its structure differs from that of cholesterol in having the double bond in the 4 : 5 position. When hydrogenated, *allo*-cholesterol yields coprosterol (coprostanol). On the other hand, *epiallo*-**cholesterol** is converted into a mixture of *epi*-cholestanol and *epi*-coprosterol.[1]

Epimerides of this series differ from the corresponding normal compounds only in the position of the OH-group relative to the rest of the molecule. The interconversion of normal and *epi*-compounds may be effected by heating them with sodium alkoxide, when an equilibrium mixture of the two forms generally results. From this mixture the compounds bearing the OH-group *cis* to methyl at position 10 can be separated by **precipitation with digitonin,** a glycoside of the saponin group. The *epi*-compounds in general do not form insoluble complexes with digitonin and this specific reaction discovered by Windaus has proved very useful in steroid chemistry for determining the arrangement of the hydroxyl group in position 3.

The difficulty of devising a nomenclature for stereoisomeric derivatives of this series has already been emphasised (p. 582), and pending a satisfactory solution of the problem Fieser [2] has suggested that *epi* and normal steroids should be distinguished by the labels (α) and (β). Nearly all the (β)-compounds are precipitated by digitonin and contain the OH group *cis* to methyl at position 10, *e.g.* cholesterol, cholestanol, coprosterol, ergosterol, etc. The (α)-compounds are not precipitated and in this class are included the *epi*-derivatives, the bile acids and androsterone. The system has been adopted by a number of workers in this field.

Ergosterol, $C_{28}H_{43}OH$, m.p. 160°, is an unsaturated alcohol containing the same carbon skeleton as cholesterol, but with an additional methyl group attached to the side chain at position 24, and with three double bonds at 5 : 6, 7 : 8, and 22 : 23. It was discovered by Tanret in ergot (p. 708), occurs in various fungi, including yeast, and is present in small amounts in most living tissues.



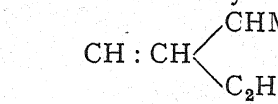
Ergosterol.

On irradiation with ultraviolet light or sunlight ergosterol is converted into a number of isomerides, accompanied by considerable decomposition. One of these has powerful anti-rachitic properties and is closely related to the vitamin D group (see under vitamins, p. 834).

Stigmasterol, $C_{29}H_{47}OH$, m.p. 170°, is found in the Calabar bean

[1] R. Schoenheimer and E. A. Evans, *J. A. C. S.*, 1936, **58**, 182; *J. Biol. Chem.*, 1936, **114**, 567. [2] *A Supplement to the Chemistry of Natural Products related to Phenanthrene*, New York, 1937, p. 399.

and the Soya bean. The side chain at position 17 is —CHMe.



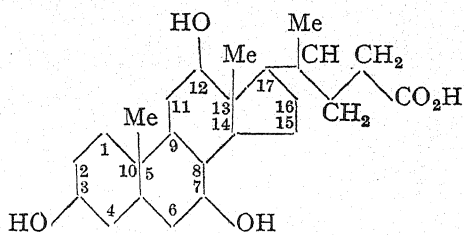
and the molecule contains a double bond at 5 : 6. Both ergosterol and stigmasterol have the same steric arrangement of hydroxyl, methyl groups and long side chain as is present in cholesterol.

Sitosterol, $C_{29}H_{49}OH$, m.p. 146°, occurs in wheat and other plants. It differs from stigmasterol only in having a fully saturated side chain.

Zymosterol, $C_{27}H_{43}OH$, m.p. 109°, can be obtained from yeast. It has been formulated by Heilbron and co-workers [1] as a cholestadienol containing double bonds at 8 : 14 and 24 : 25, and with the side chain —CHMe.$(CH_2)_2$.CH : CMe_2 attached to position 17. It is thus the first example of an unsaturated natural sterol devoid of a double bond at the 5 : 6-position. The terminal isopropylidene group is also unusual, but its presence is shown by the formation of acetone when zymosterol is ozonised. When fully saturated, zymosterol is converted into cholestanol.

The Bile Acids

Bile acids form the main constituents of the bile or secretion of the liver in vertebrate animals, the function of which is to promote the enzymic disruption of fats in the intestine. In this source they exist to a large extent in peptide union with the amino-acids glycine and taurine, and the resulting glyco- and taurocholic acids possess the physiological advantage of being more soluble in water than the unpaired acids. When the peptide bond is ruptured by enzyme or alkaline hydrolysis the bile acids are liberated as a mixture of acids which varies in composition with the animal species and with seasonal and other factors. All the compounds, however, are saturated hydroxy derivatives of the monocarboxylic acid, *cholanic acid*, those of most frequent occurrence being **cholic acid** and **deoxycholic acid.** From 100 litres of ox bile Wieland succeeded in isolating 5-6 kg. of cholic acid, 600-800 gm. of deoxycholic acid and only 1 gm. of **lithocholic acid.**



Cholic acid.

Cholic acid, 3 : 7 : 12-*trihydroxy-cholanic acid,* $C_{23}H_{36}(OH)_3.COOH$, is present in the bile of all animals. **Deoxycholic acid,** 3 : 12-*dihydroxy cholanic acid*, accompanies cholic acid in bile and has the property of forming stable co-ordination complexes with varying molecular proportions of other compounds such as palmitic, stearic and oleic acids, and also with hydrocarbons, esters, alcohols, ethers, etc. These addition complexes, which yield colloidal solutions in water, are classed together

[1] B. Heath-Brown, I. M. Heilbron and E. R. H. Jones, *J. C. S.*, 1940, 1482.

under the heading of **choleic acids.** The complex with acetic acid (alcohol or ether) contains equimolecular proportions of the two components, but as the molecular weight of the fatty acid rises its proportion in the choleic acid falls. Thus 1 molar proportion of palmitic acid combines with

Bile Acids

Name.	Position of OH groups.	m.p.	$[\alpha]_D$.	Occurrence.
Cholic acid . . .	3 : 7 : 12	195°	+37	All animals.
Bufodeoxycholic acid . .	3 : 7 : 12	—	—	Toad.
β-Phocæcholic acid . .	3 : 7 : 23	222°	+29	Seal, walrus.
Deoxycholic acid . .	3 : 12	176°	+55	All animals.
*Chenodeoxycholic acid .	3 : 7	140°	+11	Man, ox, goose, hen.
Ursodeoxycholic acid . .	3 : 7	198°	—	Bear.
Hyodeoxycholic acid . .	3 : 6	197°	—	Hog, hippopotamus.
Lithocholic acid . . .	3	186°	(+32)	Man, ox.

* Or Anthropodeoxycholic acid. This acid was first discovered in human bile and later in that of goose and hen.

8 molar proportions of deoxycholic acid. The complexes are crystalline and have definite melting points; they are remarkably stable and are not separated into their individual components by solution in water or alkali. Choleic acids containing higher fatty acids can be converted into deoxycholic acid by displacing the fatty acid with acetone, alcohol or ether, using the latter in excess, followed by vaporisation of the combined solvent from the product so obtained. Wieland has suggested that the biological function of deoxycholic acid is to convert into a more soluble colloid form compounds (*e.g.* palmitic acid) which do not normally dissolve in water, thus rendering them more readily fermented. The power of forming such complexes is also possessed by the other bile acids, although in much lower degree.

Lithocholic acid, 3-*hydroxy-cholanic acid*, is found in the bile of man and of cattle and was first isolated by H. Fischer from the gall stones of oxen.

Structure of the Bile Acids

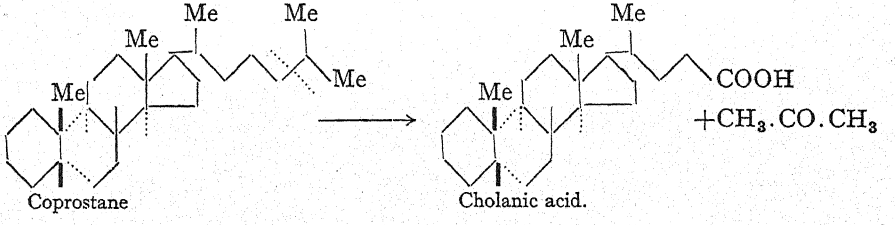
It is only possible to deal briefly with the methods by which the structures of the bile acids have been determined; for further details reference should be made to the literature.[1] One of the most useful reactions in this connection has proved to be the oxidation of the hydroxy acids to ketonic acids (CHOH→CO), using a cold solution of chromic oxide in sulphuric or acetic acid as reagent. In this manner cholic acid was dehydrogenated by Hammarsten to **dehydrocholic acid,** a triketo-compound. The keto acids are not only readily identifiable by conversion into their oximes, semicarbazones, etc., but may be made to undergo further transformation into the deoxygenated acids such as cholanic acid ($CO \rightarrow CH_2$), the formula of which is given on p. 589. Another valuable

[1] See L. Fieser, *loc. cit.*

reaction has been the distillation of the hydroxy acids in a high vacuum, when water is eliminated with the production of unsaturated acids (CH_2.CHOH→CH : CH). This change can be carried out in stages according to the number of secondary alcoholic groups in the molecule. The unsaturated acids so obtained may then be hydrogenated catalytically to yield the parent saturated compounds. Thus Wieland succeeded in converting cholic acid into cholanic acid by way of the trebly unsaturated compound cholatrienic acid.

Among other reactions, Veresterberg's *dehydrogenation process* has been employed, in which the compounds are heated to a high temperature with sulphur. Generally speaking, this treatment removes hydrogen from hydro-aromatic systems, leading to the formation of well-defined aromatic derivatives (see p. 490 for the conversion of abietic acid into retene). With the sterols and bile acid group, however, it has been found preferable to use selenium [1] in place of sulphur, the reaction then proceeding more smoothly and being accompanied by less carbonisation. The vital significance of the information gained in this way has already been indicated under cholesterol (p. 584).

Relationship of Sterols and Bile Acids.—The intimate relationship between the sterols and the bile acids was first definitely established by Windaus,[2] who showed that coprosterol, the saturated alcohol derived from cholesterol, could be converted through the corresponding chloride into the hydrocarbon coprostane (CHOH→CHCl→CH_2), which on cautious oxidation broke down into cholanic acid and acetone. This discovery first proved the nature and point of attachment of the side chain in the bile acids and the chemical identity of the ring systems in these compounds and the sterols. In the light of later knowledge on the arrangement of the rings in coprosterol and coprostane (see p. 585) it indicates that in coprostane, cholanic acid and the majority of the bile acids, rings A and B are probably fused together by *cis* linkages.



Coprostane Cholanic acid.

Windaus similarly converted cholesterol into *allo***cholanic acid,** in which rings A and B were shown to have the *trans* configuration.

A correlation of the hydroxy compounds of the cholesterol and bile acid groups was only effected later through investigations on **hyodeoxycholic acid,** which Windaus [3] had already proved to be 3 : 6-dihydroxy cholanic acid. By partial oxidation of this acid Wieland and Dane [4]

[1] O. Diels and A. Karstens, *Ber.*, 1927, **60**, 2323. [2] Windaus and Neukirchen, *Ber.*, 1919, **52**, 1915. [3] *Ann.*, 1926, **447**, 233. [4] *Z. physiol. Chem.*, 1932, **212**, 41.

converted it into 3-hydroxy-6-ketocholanic acid, which on reduction gave 3-hydroxy-*allo*cholanic acid owing to allomerisation having taken place at C5 through the influence of the adjacent keto group. This acid is isomeric with lithocholic acid and proved to be identical with the hydroxy-*allo*cholanic acid previously obtained by Windaus from cholesterol.[1] In this way the hydroxyl group in cholesterol was shown to occupy position 3.

The majority of the bile acids so far examined in detail, namely cholic acid and deoxy-, chenodeoxy-, litho- and hyodeoxy-cholic acids, belong stereochemically to the same group as coprostane and cholanic acid, in which rings A and B are believed to be joined in the *cis* position. Other cholanic acids have also been isolated, *e.g.* the two lævorotatory compounds, **ursocholanic acid** (from ursodeoxycholic acid) and **bufocholanic acid** (from bufodeoxycholic acid), and the strongly dextrorotatory **isobufocholanic acid** (from the toad poison, bufotoxin). The configurations of these acids are still unknown.

Bile acids contain the 3-hydroxyl group in the *trans* position to hydrogen at C5 and therefore belong to the (α)-series according to Fieser's nomenclature (p. 586). They are regarded as being formed in the organism by oxidative processes from cholesterol, and as the latter compound belongs to the (β)-series, the mechanism of the biological conversion raises an interesting problem.

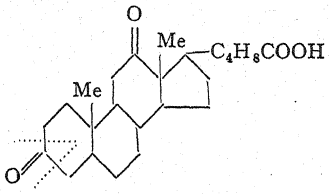
Ring Structure of the Bile Acids.—This was first firmly established as a result of the work on sterols following the formulæ advanced by Rosenheim and Wieland in 1932. But much information bearing on this point had previously been gained, especially by the oxidative degradations of bile acids and their derivatives. Some idea of the mode of attack and of the more important principles involved is given by the following necessarily brief account.

As has already been stated, analytical values obtained for cholestane and the Diels' hydrocarbon pointed to the presence of a fused 4-ring system. Thanks to the graded reactivity of the different hydroxyl and ketonic groups in the bile acids and their derivatives (position 3>7>12) it was frequently found possible to disrupt one ring without affecting the rest of the molecule, to isolate the tricarboxylic acid or mixture of isomeric acids formed and subsequently to draw conclusions as to the size of the disrupted ring from the behaviour of the acid on being heated.

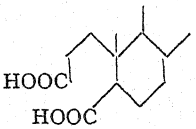
Thus deoxycholic acid yields **dehydro-deoxycholic acid** (I) on mild oxidation with chromic acid, and under more vigorous treatment the ketonic ring A breaks at the two points indicated to form **deoxybilianic acid** (II) and isodeoxybilianic acid (in II and the following formulæ only that part of the molecule corresponding to rings A and B is shown). The further behaviour of the *bilianic acids*[2] on pyrolysis (heating in high vacuum or in nitrogen) depends on the relative positions of the carboxyl groups. Blanc[3] had noted earlier that succinic acid (1 : 4-position of carboxyls) and glutaric acid (1 : 5-) gave anhydrides when heated with acetic anhydride, but that adipic acid (1 : 6-) and pimelic acid (1 : 7-) lost carbon dioxide and water to form the cyclic ketones cyclopentanone and cyclohexanone. Windaus and Wieland extended the "Blanc rule" to simple cyclic dicarboxylic acids and then applied it to the bile acid derivatives. Deoxybilianic acid (II), for example, gave rise to a ketonic acid, **pyrodeoxybilianic acid** (III), with loss of carbon dioxide. The two carboxyls in II are therefore concluded to be in

[1] The steps in this reaction were: cholesterol ⟶ cholesteryl chloride ⟶ cholestyl chloride (saturated) ⟶ 3-chloro-*allo*cholanic acid (partial oxidation of side chain) ⟶ 3-hydroxy-*allo*cholanic acid. [2] All bile acid derivatives formed in this manner are termed *bilianic acids*. [3] *C. r.*, 1907, 144, 1356.

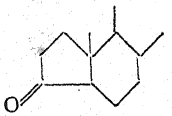
the 1 : 6-positions and to be derived from a six-membered ring in dehydro-deoxycholic acid. On oxidation of acid, III, the ketonic ring is ruptured to form an acid, IV, which on continued oxidation yields a tetracarboxylic acid, **norcilianic acid** V. The last compound contains only two rings in the molecule.



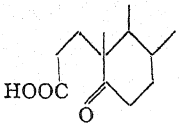
I.



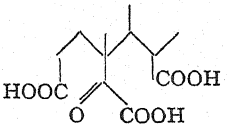
II.



III.



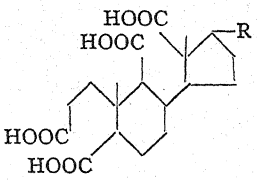
IV.



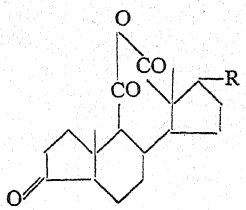
V.

By applying these methods to different types of bile acids it was found possible to open each of the rings A, B and C, although ring D, which never contains an attached hydroxyl group, could not be disrupted. Rings B and C, however, gave rise to false deductions on application of Blanc's rule, and it was discovered later that the rule is not reliable if the side chains containing the carboxyl groups are linked to different ring systems. **Choloidanic acid,** for example (shown in skeleton form in VI), on pyrolysis

VI.



VII.



is converted into VII. Both pairs of carboxyls are in the 1 : 6 positions, but the pair derived from ring C form an anhydride, and it was at one time wrongly concluded that they were therefore of the 1 : 5-type and that ring C was five-membered. It will be seen that these carboxyls are joined to two independent ring systems (B and D), linked only through the single bond between positions 8 and 14.

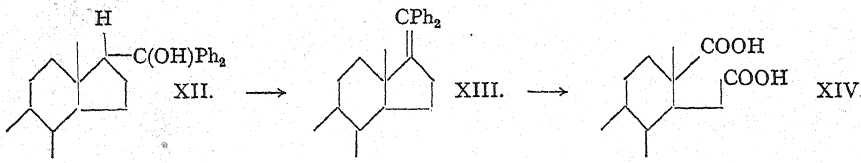
The most resistant ring, D, was opened by Wieland after cholanic acid (formula, p. 589) had been converted by step-wise degradation of the side chain into **aetiocholanic acid.** For this purpose cholanic ester was treated with phenyl magnesium bromide (or other Grignard reagent) to form the carbinol, which on oxidation with chromic oxide broke down to *norcholanic acid* VIII and benzophenone. The latter acid on repetition of the process was converted into *bisnorcholanic acid* IX and this by a third application of the Grignard reagent followed by dehydration of the carbinol gave an unsaturated hydrocarbon [1] X, which on oxidation yielded **aetiocholanic acid** XI. In the following scheme X=the cholane residue $C_{19}H_{31}$; Ph=phenyl; Me=methyl.

$$X.CHMe.CH_2.CH_2.COOEt \longrightarrow X.CHMe.CH_2.CH_2.C(OH)Ph_2 \longrightarrow X.CHMe.CH_2.COOH \text{ (VIII)}$$

$$\longrightarrow X.CHMe.COOH \text{ (IX)} \longrightarrow X.CMe:CPh_2 \text{ (X)} \longrightarrow X.COOH \text{ (XI)}.$$

[1] By ozonisation of this hydrocarbon a methyl ketone, $X.CO.CH_3$, was later obtained by Butenandt, which on reduction by the Clemmensen method gave 17-methyl-aetiocholane, $X.CH_2.CH_3$. This compound proved to be identical with pregnane prepared from the natural product pregnanediol (see section on sex hormones).

The opening of ring D was then effected in the following steps. Aetiocholanic ester, when treated with phenyl magnesium bromide, formed a carbinol (XII), which was dehydrated to *diphenyl-aetiocholene* XIII. This last on oxidation gave a dicarboxylic



acid, **aetiobilianic acid** XIV, indicating that ring D had opened. The conversion of aetiobilianic acid into an anhydride on pyrolysis led by application of Blanc's rule to the conclusion that this ring is five-membered.

THE SEX HORMONES

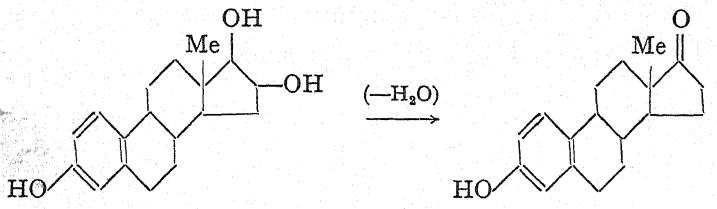
All the sexual processes of the organism are now known to be initiated and maintained under the stimulus of a number of hormones, each of which can be characterised by definite biological tests. The primary agent appears to be the secretion of the anterior lobe of the pituitary gland, containing the as yet unidentified **gonadotropic hormone(s).** Under the influence of this secretion other hormones are formed in the ovaries or testes which control the growth and functioning of the reproductive organs. Three main groups of such hormones have been distinguished and the corresponding active principles isolated. In the female these are the **follicular hormones,** which induce the state of œstrus (heat), and the **hormones of the corpus luteum** (yellow body), which govern the processes of pregnancy. The **male sex hormones** influence the development of the genital tract and accessory male characteristics, such as the comb and wattles of the cock and the horns of the stag. As the result of a brilliant series of researches carried out independently by several groups of workers—mainly in the laboratories of Butenandt, Doisy, Marrian, Ruzicka and their collaborators—it has been possible in the brief period of six years to isolate the individual hormones, establish their structures and devise methods of preparing them in sufficient quantities for biological research and use in medicine.

Follicular Hormones.—The first chemical advance was made in this group largely owing to the introduction of the Allen-Doisy test. These workers prepared cell-free extracts of ovaries, which on being injected into castrated mice or rats induced œstrus. The active agent was therefore chemical in nature and with the development of a method of determining the minimum dose necessary for the change a satisfactory quantitative method of estimating the strength of the hormone content (in mouse or rat units) of any given preparation became for the first time possible. The use of this test by Aschheim and Zondek in 1927 led to the important discovery that the hormone, previously obtained in minute quantities and very crude form from the follicular fluid (ovaries), was present in the pregnancy urine of women, from which a much purer active preparation could be obtained by extraction with benzene, preferably after acid

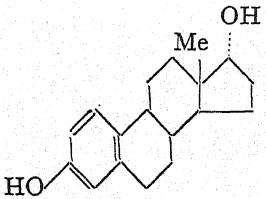
hydrolysis. Shortly afterwards, the isolation of a pure crystalline hormone, *œstrone*, was announced independently in 1929 by Doisy [1] in America and Butenandt [2] in Germany.

Œstrone, $C_{18}H_{22}O_2$, is a phenolic ketone, m.p. 259°, $[\alpha]_D + 158{\cdot}5°$. Like so many other members of this group it exists in polymorphic forms. The average content of the urine source is only about 1 mg. per litre (ca. 15,000 m.u. being eliminated per diem) of which only a fraction can be extracted. A better source was discovered in 1930 by Zondek in the urine of pregnant mares (1,000,000 m.u. per diem), and surprisingly enough an even richer one in the urine (1,700,000 m.u. per diem) and testes of stallions. The curious phenomenon of a higher excretion of the female sex hormone by the male is found only among the horse tribe, including ass and zebra. Small quantities of the follicular hormones also occur in plants, œstrone having been obtained from palm kernels and the related compound, *œstriol*, from female willow flowers.

Œstriol, $C_{18}H_{24}O_3$, another follicular hormone, was isolated by Marrian [3] in London soon after the discovery of œstrone. It melts at 280°, has $[\alpha] = +30°$, and shows considerably less œstrogenic activity than œstrone although the effect is more protracted. From the analysis figures Butenandt concluded that œstriol was a hydrate of œstrone and showed that it could be converted into the latter by heating with potassium hydrogen sulphate followed by distillation in a high vacuum. The relationship was clarified by Marrian and Haslewood,[4] who dehydrated the methyl ether of œstriol and obtained the methyl ether of œstrone.



Œstriol Œstrone

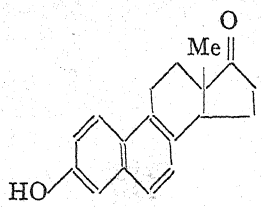


α-Œstradiol.

The catalytic reduction of œstrone in alkaline medium [5] leads to the formation of two **œstradiols**, α and β, m.p. 176 and 223° respectively. The first of these compounds yields an insoluble product with digitonin

[1] Doisy, Veler and Thayer, *Am. J. Physiol.*, 1929, **90**, 329; *J. Biol. Chem.*, 1930, **86**, 499; **87**, 357. [2] Naturwissenschaften, 1929, **17**, 879; *Z. physiol. Chem.*, 1930, **188**, 1. [3] *Biochem. J.*, 1930, **24**, 435. [4] *Biochem. J.*, 1932, **26**, 25. [5] Schwenk and Hildebrandt, *Naturwiss.*, 1933, **21**, 177.

and according to Fieser's scheme (p. 586) is therefore provisionally represented as a (β)-compound, with OH at C_{17} in the *trans* position to methyl at C_{13}. **α-Œstradiol** is an exceedingly potent œstrogenic compound and is present in the ovaries and in follicular fluid.[1] It is possibly the chief follicular hormone. β-Œstradiol is comparatively inert.

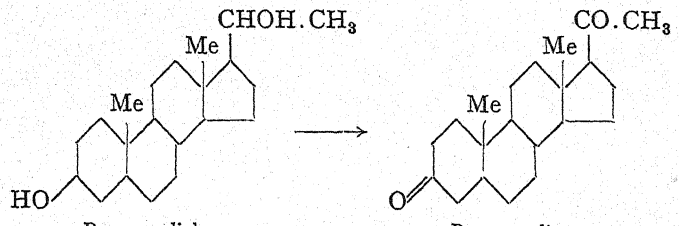


Equilenin.

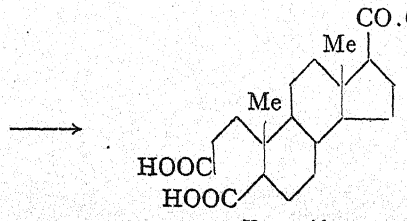
Still other œstrogenic hormones, **equilin**, **hippulin** and **equilenin** have since been isolated from urine of pregnant mares by Girard in Paris. Equilenin, which is not found in human urine, appears to be formed by the dehydrogenation of œstrone.

Structures of the Follicular Hormones.—A physiologically inactive companion compound of œstrone named **pregnanediol** (m.p. 233-235°) was obtained by Marrian in 1929 and was later characterised by Butenandt as a completely saturated substance containing two secondary alcoholic groups, since on oxidation it yielded a diketone *pregnanedione*. Pregnanediol has proved to be a key compound in establishing the chemical structures of this group. Analytical data indicated that the molecule was built up of four fused rings, suggesting a possible relationship to the bile acids. This was borne out by more vigorous oxidation, when the ketone gave rise to a keto-dicarboxylic acid (*cf.* bilianic acids), which on being heated lost carbon dioxide to form a diketone. By Blanc's rule one oxygen was thus deduced to have been attached originally to a 6-membered ring. The other was concluded to be in a side chain, since all three compounds gave the iodoform reaction (*cf.* p. 133).

On this basis and by analogy with the sterols and bile acids Butenandt in 1930 expressed the first two of these changes by the following formulæ



Pregnanediol Pregnanedione



Keto-acid.

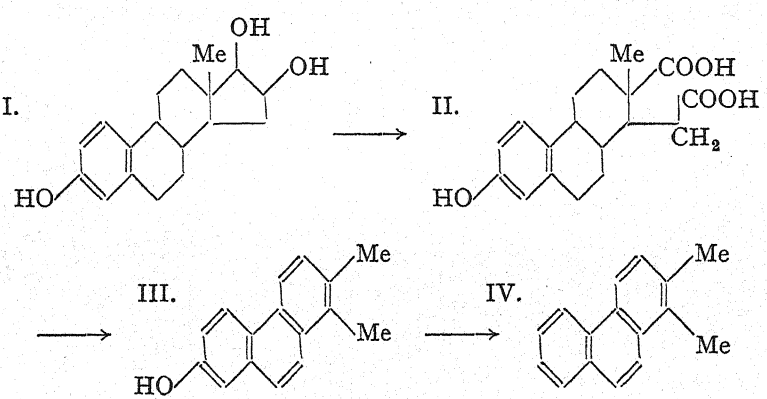
(here modified according to later views on the structure of cholane).

[1] MacCorquodale, Thayer and Doisy, *J. Biol. Chem.*, 1936, **115**, 435.

Subsequently the dione was reduced by the Clemmensen method to a saturated hydrocarbon, pregnane, $C_{21}H_{36}$. The relationship of this compound to the bile acid series was completely established by its synthesis from Wieland's bisnorcholanic ester, by way of the unsaturated hydrocarbon $C_{19}H_{31}.CMe:CPh_2$ (see formula X, p. 591). Butenandt showed that the latter on ozonisation [1] gave the ketone $C_{19}H_{31}.COCH_3$, which on reduction (Clemmensen) was converted into *17-ethyl-ætiocholane*, $C_{19}H_{31}.CH_2.CH_3$, identical in all respects with pregnane. These compounds therefore belong to the coprostane group with rings A and B joined by *cis* linkages. No biological deductions can be drawn from this point, however, because other workers subsequently discovered the stereoisomeric allo*pregnanediol* in urine of pregnancy. The position (3) at which the remaining oxygen atom is attached was not determined until later.

In 1932 Butenandt,[2] Marrian and Haslewood [3] advanced a formula for œstrone based on the bile acid structures. The last two workers and also Doisy [4] had examined the fusion of œstriol (I) with alkali, and shown that a phenolic dicarboxylic acid (II) resulted. Such a change could be explained on the assumption that the two alcoholic hydroxyls in œstriol were attached to adjacent carbon atoms, and that a break between these points led to the opening of a ring. The dicarboxylic acid on pyrolysis gave an anhydride and not a ketone, hence the ring is presumably a 5-membered one.

By fusion with selenium Butenandt [5] found that the dicarboxylic acid readily passed into a *dimethyl-phenanthrol* (III), which on distillation with zinc dust yielded 1 : 2-*dimethyl-phenanthrene* (IV). The same



compound has been obtained by selenium dehydrogenation of ætiobilianic acid, thus providing a link with the bile acid series. The structure of IV was proved by its synthesis, using a method due to Haworth.[6]

[1] Butenandt, *Ber.*, 1931, **64B**, 2529. [2] *Nature*, 1932, **130**, 238; *Z. angew. Chem.*, 1932, **45**, 655. [3] *J. S. C. I.*, 1932, **51**, 277 T. [4] MacCorquodale, Thayer and Doisy, *J. Biol. Chem.*, 1933, **99**, 327. [5] Butenandt, Weidlich and Thompson, *Ber.*, 1933, **66**, 601. [6] R. D. Haworth, *J. C. S.*, 1932 and 1934.

More detailed proof, however, was soon supplied by the work of Haworth and of Cook. The former [1] synthesised 1 : 2-dimethyl-7-methoxy-phenanthrene, which was found to be identical with the methyl ether of Butenandt's compound (III), thus establishing the position of the hydroxyl group. Cook [2] achieved a remarkable synthesis of 7-methoxy-1 : 2-cyclopentenophenanthrene (V), containing the fused 5-membered ring; and also isolated this compound from œstrone by methylation, elimination of the ketonic group by reduction, followed by dehydrogenation with selenium. The final points, the positions of the angular methyl group and of ketonic oxygen, were eventually established by Cohen, Cook and Hewett.[3] Methylated œstrone was treated with methyl magnesium iodide, converting the keto group into an alcoholic group; the alcohol VI was then dehydrated (VII) and the resulting unsaturated compound hydrogenated. Final dehydrogenation with selenium gave *7-methoxy-3′ : 3′-dimethyl-1 : 2-cyclopentenophenanthrene*, the structure of which was proved by synthesis. These changes can only be explained by assuming that VI contains a tertiary alcoholic group (at C_{17}) linked to a carbon atom adjacent to a quaternary carbon, when rearrangements such as the wandering of methyl from C_{13} to C_{17} are to be expected. This conclusion is confirmed by the fact that a similar migration of a methyl group was observed to occur when œstradiol, which had been methylated in position 3, was dehydrated with zinc chloride and then dehydrogenated, forming 7-methoxy-3′-methyl-1 : 2-cyclopentenophenanthrene (VIII). In this case the methyl group can only have come from the angular position at C_{13} and must be present as such in œstrone from which the œstradiol was prepared.

V.

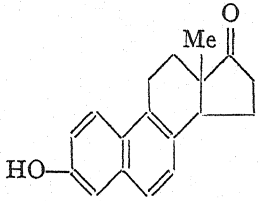
VI. → VII.

VIII.

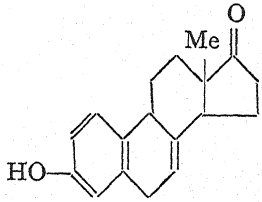
The above work of Cohen, Cook and Hewett also threw light on the structures of equilenin and equilin, both of which were converted into 7-methoxy-3′ : 3′-dimethyl-1 : 2-cyclopentenophenanthrene. Their resemblance to œstrone proves that these hormones have a similar arrangement of hydroxyl, methyl and keto groups in a steroid nucleus.

[1] Haworth and Sheldrick, *J. C. S.*, 1934, 864. [2] A. Cohen, J. W. Cook, Hewett and Girard, *J. C. S.*, 1934, 653. [3] *J. C. S.*, 1935, 445.

Since equilenin forms a picrate it presumably also contains a naphthalene nucleus, leading to the formula given below. This compound has now been synthesised in its optically active form by Bachman, Cole and Wilds, *d*-equilenin proving to be thirteen times as potent as its mirror-image isomeride.[1] The actual position of the second double bond in ring B of



Equilenin

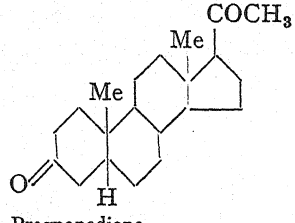


Equilin.

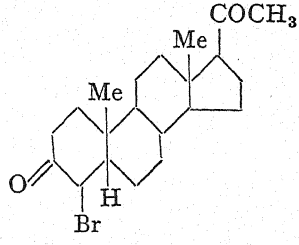
IX.

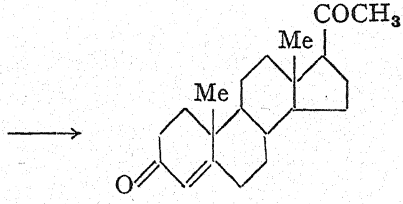
equilin is not yet known with certainty, it is probably either 7 : 8 (IX) or 8 : 9.

Hormone of the Corpus Luteum.—The isolation of the pure crystalline **progesterone,** $C_{21}H_{30}O_2$, was achieved almost simultaneously by Butenandt,[2] Slotta [3] and Allen,[4] using corpus luteum tissue from sow ovaries. Only one hormone appears to exist, but it occurs in two polymorphic forms melting at 128° and 121° respectively ($[\alpha]_D$ +192°). It was found to be an unsaturated diketone and from an investigation of its absorption in the ultraviolet region it was concluded [5] that it contained a double bond in the $\alpha\beta$-position to a carbonyl group. An X-ray analysis of the crystalline compound gave results in agreement with a steroid structure, and Slotta formulated the hormone as Δ^4-pregnene-



Pregnanedione





Progesterone.

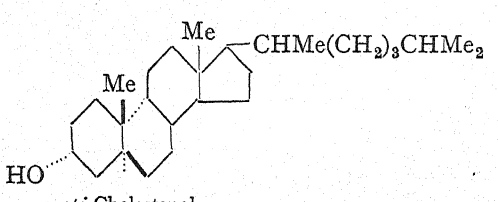
dione-(3 : 20). This was subsequently confirmed by a synthesis of progesterone from stigmasterol carried out by Butenandt [6] and Fernholz [7]

[1] W. E. Bachmann, W. Cole and A. L. Wilds, *J. A. C. S.*, 1940, **62**, 824. [2] *Wien. Klin. Wochsch*, 1934, **30**., 934. [3] Slotta, Ruschig and Fels, *Ber.*, 1934, **67**, 1270. [4] W. M. Allen and Wintersteiner, *Science*, 1934, **80**, 190. [5] Slotta, Ruschig and Fels, *Ber.*, 1934, **67**, 624; Wintersteiner and Allen, *J. Biol. Chem.*, 1934, **107**, 321. [6] *Ber.*, 1934, **67**, 1901, 2085. [7] *Ibid.*, pp. 1855, 2027.

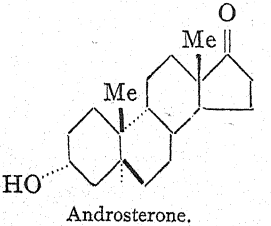
independently. Another and shorter preparation which proves the constitution was made known about the same time by Butenandt.[1] Pregnanediol (see p. 594) was oxidised to the saturated ketone, pregnanedione, which was brominated and hydrogen bromide subsequently removed from the product by heating with pyridine.

The Male Sex Hormones.—The successful isolation of the testicular hormones also rested upon the introduction of quantitative methods of biological assay, by which the activity of a given preparation could be determined. One such method involves injecting the extract into capons, and measurement of the comb growth by use of a shadowgraph (*Gallagher-Koch*); another is based on the effect of injections on the development of the seminal vesicles of castrated immature rats (*Butenandt-Tscherning*).

Androsterone.—Using the above methods of assay, Butenandt and Tscherning [2] in 1931 extracted the first male sex hormone, **androsterone**, $C_{19}H_{30}O_2$, from male urine which had previously been boiled with hydrochloric acid. The compound, m.p. 182-183°, proved to be a ketonic alcohol but was only isolated in exceedingly small quantities. On the assumption that it was a steroid, Butenandt suggested a formula which



epi-Cholestanol



Androsterone.

in 1933 was confirmed and defined in a stereochemical sense by Ruzicka.[3] The latter found that the side chain in cholestanyl acetate could be oxidised away with chromic oxide, and that the acetate of a ketone could be obtained in small yield. On hydrolysis the acetate gave a hydroxy ketone of the structure proposed by Butenandt. The product from cholestanol was not androsterone, but on extending the degradation to the other known stereo-isomers of cholestanol a compound was obtained from *epi*-cholestanol which was identical with the natural hormone. Thus Butenandt's general formula was confirmed and the spatial arrangements of the hydroxyl group and of rings A and B were determined. In this way the relationship between a sex hormone and the sterols was for the first time definitely established.

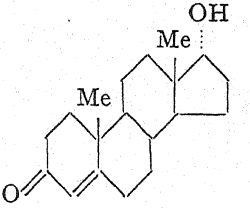
Another preparation of androsterone starting from the more accessible cholesterol has been carried out by Marker [4] in the following steps, which must involve at one stage an optical inversion of the group at C3:

Cholesterol $\longrightarrow$ cholesteryl chloride $\xrightarrow{2H}$ cholestyl chloride (saturated compound) $\xrightarrow{CrO_3}$ α-chloroandrosterone $\xrightarrow{\text{Potass. acetate}}$ acetyl derivative $\xrightarrow{\text{hydrolysis}}$ androsterone.

[1] *Ber.*, 1934, **67**, 1901, 2085. [2] *Nature*, 1932, **130**, 238. [3] Ruzicka, Goldberg and Brüngger, *Helv.*, 1934, **17**, 1389. *Chem. Rev.*, 1937, **20**, 69. [4] *J. A. C. S.*, 1935, 1755, 2358.

Androsterone isolated from urine was found to differ markedly from testicular extract when bio-assays were carried out by the two methods. Equivalent doses of the two extracts as measured by the comb test, did not give equal results with castrated rats, from which the testicular extract appeared to be several times more active. Further investigation led to the isolation from urine of **dehydro-androsterone**, resembling androsterone in structure but with a double bond in the 5 : 6-position. This, however, proved even less active as determined by the rat test. Neither of these compounds could therefore be regarded as the chief testicular hormone.

At this stage, in 1935, a crystalline hormone, **testosterone**, m.p. 154·5°, was isolated from testes by Laqueur and David.[1] It was found to be very potent, but as in the case of the corpus luteum hormone, progesterone, the potency was destroyed by heating the compound with alcoholic alkali. This similarity in chemical properties was traced to a similar (4 : 5-) position of the double bond, as is seen in the annexed formula due to David. The spatial arrangement of the hydroxyl group at C_{17} is provisional.



Transmutations of Cholesterol in the Animal Organism

A detailed study of the various steroid derivatives which have been identified in the body or in urine suggests very strongly that they all arise from the biochemical oxidation of cholesterol. Thus the side chain, $—CHMe^{(b)}CH_2.CH_2.CH_2^{(a)}CHMe_2$, may undergo oxidative disruption at point (a), with removal of the isopropylidene group and formation of an acid, $—CHMe.CH_2.CH_2.COOH$. Subsequent minor alterations in the nucleus can then lead to the production of bile acids. Or the side chain may break at point (b), leaving a group $—CO.CH_3$ linked to position 17. The resulting ketone by further metabolic changes may give rise to compounds of the type of progesterone and pregnanediol. As a third possibility, the side chain may be completely oxidised away, leaving a ketonic oxygen atom attached to the nucleus. Such a compound can be readily transformed into testosterone, androsterone and the related œstradiol and equilin groups. There is evidence that such oxidative and reductive reactions actually occur in the body, and schemes representing possible stages by which the hormones and bile acids may be produced from cholesterol have been advanced by Butenandt and by Ruzicka. It is a striking fact that apart from two or three exceptions all the necessary intermediates have already been shown to be present in the organism.

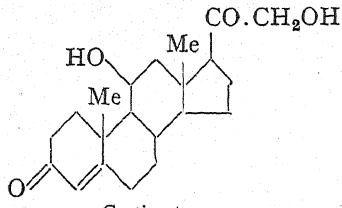
Hormones of the Adrenal Cortex

The secretion from the adrenal cortex, a small gland lying near the kidneys, contains hormones which are essential to life. They play a part

[1] *Z. physiol. Chem.*, 1935, **233**, 281.

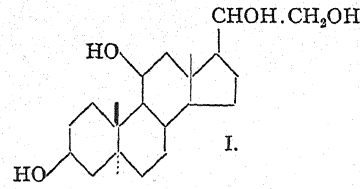
in regulating the amount of fluid in the vascular system and appear to be also concerned in sex development. Extracts of the gland are used medicinally in Addison's disease.

A number of these hormones have been isolated,[1] chiefly by Kendall and Reichstein, the most important one being **corticosterone**, $C_{21}H_{30}O_4$, a Δ^4-pregnene-11 : 21-diol-3 : 20-dione. The characteristic activity of the compound is largely due to the $CO.CH_2OH$-group in position 17. Similar activity is found in 21-hydroxy-progesterone, which has been prepared from stigmasterol and differs from corticosterone only in the absence of an 11-hydroxy group.

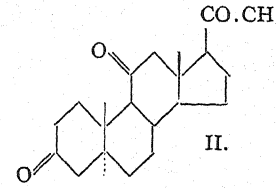


Corticosterone.

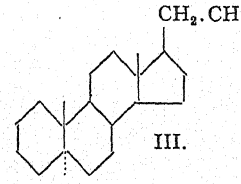
Proof of the steroid structure of corticosterone has been provided by its transformation into *allo*pregnane in the following steps[2]: The hormone was reduced to the saturated tetrol I (angular methyl groups are omitted): oxidation with periodic acid converted



I.



II.



III.

the side chain at 17 into CHO, leaving the rest of the molecule unchanged: treatment with methyl magnesium bromide gave an alcohol ($CHO \longrightarrow CHOH.CH_3$), which on oxidation with chromic acid yielded a ketone II: this last when reduced with amalgamated zinc was converted into *allo*pregnane III.

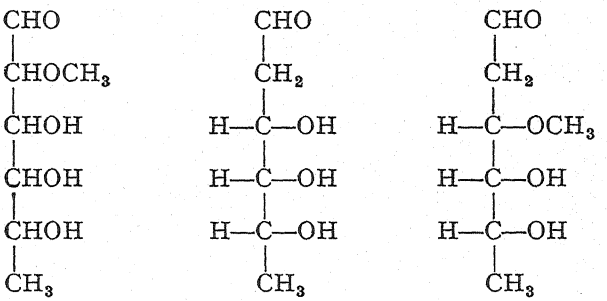
The Cardiac Poisons

Under this heading are included a number of plant glycosides such as *digitalin* and *strophanthidin*. Some of these are valuable medicinally when employed in small doses by intravanous injection, and lead to a strengthening of the heart action. Larger doses are fatal, causing stoppage of the heart, and certain natural products of this group have been used as arrow poisons by native tribes.

The cardiac poisons occur chiefly in members of the *Apocynaceæ* and *Scrophularineæ*, most of the therapeutically important drugs being prepared from the *Digitalis* (foxglove) group of the latter order. As

[1] See Wintersteiner and Smith, *Ann. Rev. Biochem.*, 1938, 7, 253; Miescher, *Angew. Chem.*, 1938, 51, 551. [2] Steiger and Reichstein, *Helv.*, 1938, 21, 161.

glycosides, the plant principles are hydrolysed by enzymes or acids to form the corresponding aglycones, known as **genins,**[1] and a mixture of sugars. Amongst the sugars isolated are glucose, rhamnose and a number of others which have not been encountered elsewhere in nature, such as the methylated methylpentose, *digitalose*, and various α-desoxysugars, including *digitoxose* and *cymarose*.



Digitalose Digitoxose Cymarose.

The chemistry of these compounds has proved much more complex than was at one time supposed. Earlier workers had succeeded in extracting from the seeds of *Digitalis purpurea* (purple foxglove) the water-soluble glycoside **digitalin,** and from the leaves digitalin and the alcohol-soluble glycosides **digitoxin** and **gitoxin.** From *Digitalis lanata* had been obtained gitoxin and **digoxin.** Recent work by Stoll, however, has shown that these compounds are not present in the free state in the plant, but result from the enzymic hydrolysis of still more complex glycosides. By use of special methods of extraction he isolated from the leaves of *D. lanata* three **digilanides,** distinguished as A, B and C. Their relationship to the above glycosides is shown by the following transformations :

Digilanide A $\xrightarrow[\text{hydrolysis}]{\text{mild alk.}}$ Purpurea glycoside A + acetic acid
(present also in *D. purpurea*)

Purpurea glycoside A $\xrightarrow[\text{from leaves}]{\text{enzyme}}$ digitoxin + glucose

digitoxin $\xrightarrow{\text{acid hydrol.}}$ digitoxose + **digitoxigenin**
(a desoxy-sugar) (an aglycone)

The digilanide may also be decomposed by direct acid hydrolysis, as follows :

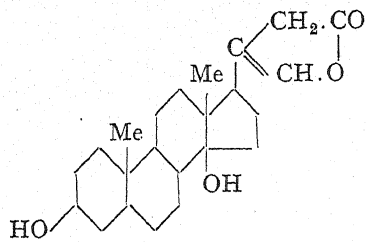
Digilanide A ⟶ digitoxigenin + digitoxose + glucose + acetic acid.
$C_{49}H_{76}O_{19}$ $C_{23}H_{34}O_4$ (3 mols.)

Digilanides B and C behave similarly but yield the aglycones **gitoxigenin** ($C_{23}H_{34}O_5$) and **digoxigenin** ($C_{23}H_{34}O_5$) respectively.

The sugar-free genins were investigated by Windaus and subsequently in greater detail (1922-1934) by W. A. Jacobs. When the structures of the sterols and bile acids were established about 1934, the work of Jacobs

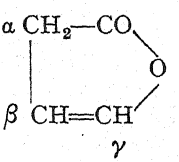
[1] The sugar-free compounds are of no value in medicine.

enabled correct formulæ to be deduced for a number of the more important genins. A typical structure is that shown for **digitoxigenin,** which in addition to hydroxyls at positions 3 and 14, contains at position 17 the lactone ring characteristic of the cardiac poisons. This ring can be opened by titration with alkali, thus permitting an estimate of the molecular weight of the compound.

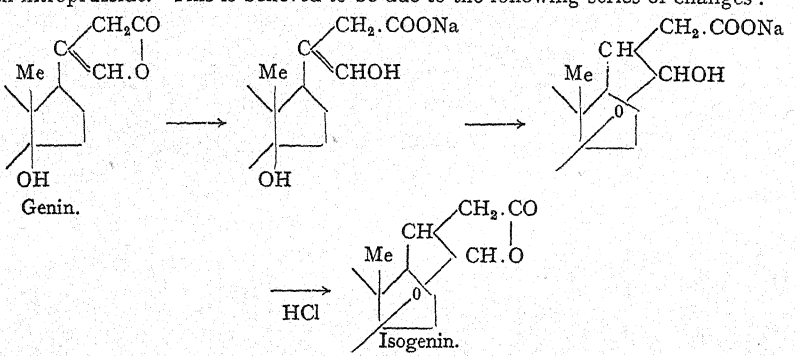


Digitoxigenin.

The unsaturated lactonic group is responsible for the deep red coloration given when a genin dissolved in pyridine is treated with an alkaline solution of sodium nitroprusside (*Legal's test*). No such colour is given with the dihydro-genins formed by reduction, in which the lactone ring has been saturated. Experiments carried out by Jacobs with simpler lactones showed that Legal's test is peculiar to $\beta\gamma$-unsaturated γ-lactones. It was also found that $\beta\gamma$-unsaturated lactones having a substituent in the γ-position cannot be hydrogenated without rupture of the ring, but that β-substituted lactone rings do not open under this treatment. Since the dihydrogenins prepared from cardiac poison genins retain the ring structure it is concluded that the original genins contain $\beta\gamma$-unsaturated lactone rings with the β-carbon atoms attached to position 17.



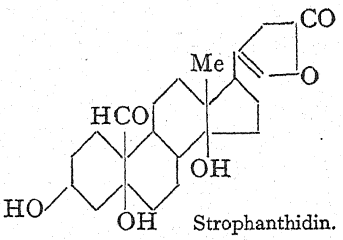
A further peculiarity of the lactone ring is that it is opened by the action of alcoholic alkali, but that the recovered product is an **isogenin** which no longer gives a coloration with nitroprusside. This is believed to be due to the following series of changes :



Strophanthidin (from species of *Strophanthus*) contains an aldehyde group in place of the more usual methyl at position 11, and there is an additional hydroxyl at position 5. The isolation of the Diels' hydrocarbon by the selenium dehydrogenation of strophanthidin (Elderfield and Jacobs, 1934) first suggested a relationship between the cardiac poisons and the sterols.

The structures of other closely related compounds are believed to be as follows : **gitoxigenin,** 3 : 14 : 16-trihydroxy-10 : 13-dimethyl- ; **digoxi-**

genin, 3 : 11 : 14-trihydroxy-10 : 13-dimethyl- ; **uzarigenin**, 3 : 8 : 14-trihydroxy-10 : 13-dimethyl- ; and **periplogenin**, 3 : 5 : 14 - trihydroxy - 10 : 13 - dimethyl-. **Scillaridin A**, obtained from the sea onion, *Scilla maritima*, appears to be of somewhat different structure, having a six-membered lactone ring and no hydroxyl at position 3.



Strophanthidin.

Conclusive proof of the cyclopentenophenanthrene nucleus in the cardiac poisons is given by the work of Tschesche, who degraded uzarigenin to ætio*allo*cholanic acid. Jacobs and Elderfield similarly degraded digitoxigenin to ætiocholanic acid. As the great majority of the cardiac aglycones can be correlated with digitoxigenin, it may be concluded that these probably contain a *cis* fusion of rings A and B. Uzarigenin apparently has the alternative arrangement.

Toad Poisons

Active principles with an action on the heart resembling that of digitalis, although less persistent, have long been known to be present in the parotid glands and skin of the toad (Latin, *bufo*). The secretions of the glands, which are situated behind the eyes, were investigated chiefly by Wieland and found to contain a mixture of **bufotoxins** (conjugated genins), **bufagins** (genins), together with sterols, adrenaline and other alkaloid bases. The cardiac activity arises from the bufotoxins and bufagins.

These compounds are related chemically to the cardiac poison group, being derived from a steroid nucleus having at position 17 a six-membered and generally unsaturated lactone ring such as is found in Scillaridin A. They are not present in the secretion as glycosides but as suberylarginine esters of the genins. The best characterised compound is **bufotoxin** (from *Bufo vulgaris*), $C_{40}H_{62}O_{11}N_4$, which can apparently lose suberylarginine in the organism to yield **bufotalin**, $C_{26}H_{36}O_6$. With normal hydrolysis, *e.g.* hydrochloric acid, bufotalin breaks down into **bufotalien**, $C_{24}H_{30}O_3$ (an anhydro-compound), acetic acid and water. **Gamabufogenin**, $C_{24}H_{34}O_5$, has been isolated from the skins of Japanese toads.

Saponins

Saponins are plant glycosides having the property of forming colloidal solutions with water which foam on being shaken. This definition also includes the cardiac poisons, but owing to their characteristic physiological effects these compounds are grouped separately. Saponins may be recognised by their strong hæmolytic action, even in high dilution, which results in the liberation of hæmoglobin from the red corpuscles of the blood. When taken in small quantities by the mouth they are not poisonous, but they are relatively more harmful to lower organisms and are employed by primitive tribes for poisoning fish without rendering

them inedible. In earlier times saponins were used for washing purposes. Their property of forming insoluble complexes with equimolecular proportions of certain other steroids (as well as various higher alcohols, phenols and thiophenols) has already been mentioned on p. 586. Digitonin has thus proved a valuable if expensive reagent for determining the configuration of hydroxyl attached to the steroid nucleus, especially in position 3.

Saponins are found as mixtures in soapwort (*Saponaria officinalis*), smilax and plants of the gourd family, and in smaller quantities in digitalis plants, where they accompany the cardiac poison glycosides. From the chemical standpoint they fall into at least two groups. Saponins from digitalis glycosides yield Diels' hydrocarbon [1] on dehydrogenation with selenium and therefore belong to the steroids; the majority of other saponins give 1 : 2 : 7-trimethyl-naphthalene [2] (*sapotalene*) and thus contain a different ring system.

On acid hydrolysis the saponins decompose to form a sapogenin and several molecular proportions of sugars, *e.g.*

Digitonin, $C_{56}H_{92}O_{29}$,[3] from *Digitalis purpurea*, breaks down to **digitogenin**, $C_{27}H_{44}O_5$, galactose (4 mols.) and xylose.

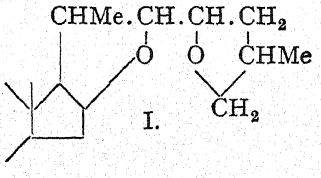
Tigonin, $C_{56}H_{92}O_{27}$, from *D. purpurea* and *D. lanata*, gives **tigogenin**, $C_{27}H_{44}O_3$, glucose (2 mols.), galactose (2 mols.) and rhamnose.

Gitonin, from *D. purpurea*, forms **gitogenin**, $C_{27}H_{44}O_4$, galactose (3 mols.) and a pentose.

Sarsasaponin, from *Radix sarsaparillæ*, forms **sarsasapogenin**, $C_{27}H_{44}O_3$.

It will be noted that the sugars liberated are of the usual types encountered in nature, in which respect the digitalis saponins differ from the accompanying cardiac poisons.

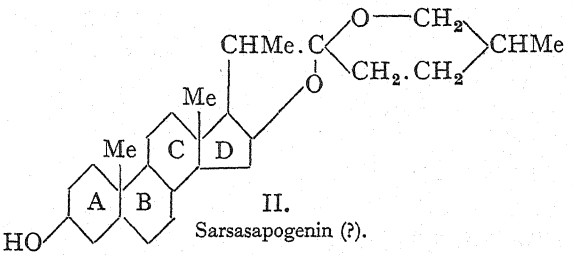
The best investigated saponins are those of the digitalis group. Jacobs and Simpson dehydrogenated gitogenin and sarsasapogenin with selenium and isolated Diels' hydrocarbon; tigogenin [4] was degraded to ætio*allo*bilianic acid, and sarsasapogenin [5] to ætiobilianic acid. When treated with hydrogen chloride in acetic acid (or on selenium dehydrogenation) the sapogenins yield a hexyl methyl ketone, indicating the presence of an 8-carbon group at position 17. The elucidation of the nature of this characteristic group, however, has proved a difficult problem. It was formulated by Tschesche [4] as in I, which accounts satisfactorily for the formation of a bilianic acid by opening of ring D between positions 16 and 17. Recent work by Marker and co-workers,[6]



I.

[1] Jacobs and Simpson, *J. A. C. S.*, 1934, 56, 1424. [2] Ruzicka and co-workers, *Helv.*, 1932, 15, 431, 1496; 1934, 17, 442. [3] Formulæ of saponins and their genins given here are to be regarded as provisional. [4] Tschesche and Hagedorn, *Ber.*, 1935, **68**, 1412, 2217; 1936, **69**, 797. [5] S. N. Farmer and G. A. R. Kon, *J. C. S.*, 1937, 414. [6] R. E. Marker and E. Rohrmann, *J. A. C. S.*, 1939, **61**, 846.

however, emphasises the hydrolysis of the side chain in acid media and its stability towards alkali. As a result they advanced the alternative formula II for sarsasapogenin, in which it is represented as having a



II.
Sarsasapogenin (?).

protected (ketal) carbonyl group. This structure is also in agreement with the reaction of sarsasapogenin with alkyl magnesium halides to form products containing two esterifiable hydroxyl groups.[1] Sarsasapogenin and tigogenin are both precipitated by digitonin and are therefore classed as (*β*)-compounds, having the hydroxyl group at C3 in *cis* position to methyl at C10.

[1] *J. A. C. S.*, 1940, **62**, 900.

PART III

Heterocyclic Compounds

REFERENCE has repeatedly been made to the occurrence of cyclic compounds in which the ring systems—unlike those of the carbocyclic series—are composed of other elements in addition to carbon. These are generally classed under the name of **heterocyclic compounds.** Owing to their close relationship to members of the aliphatic series, certain derivatives of this type have already been described in the aliphatic section, *e.g.* ethylene oxide, diazo-methane, lactones, anhydrides, cyanuric acid and purine compounds. These are readily prepared from open-chain compounds, and by rupture of the ring the latter are easily regenerated. The ring systems of the compounds about to be described are distinguished by greater stability, *i.e.*, they are less readily ruptured. Most of such rings resemble the benzene nucleus in containing several unsaturated linkages, and in chemical behaviour the heterocyclic compounds also possess many points in common with those of the benzene series.

Heterocyclic systems are known in great variety, and their study forms one of the most interesting branches of organic chemistry. Only derivatives of ring systems containing carbon in union with the elements oxygen, sulphur and nitrogen will be considered here. Compounds of this type in which sulphur has been replaced by selenium, and others which contain arsenic and phosphorus, have also been prepared. As in the case of carbocyclic compounds, a distinction is again drawn between rings containing three, four, five, six and a still higher number of atoms. The elements which participate with carbon in ring formation are sometimes termed **hetero-atoms,** and according to the number of these present we speak of mono-, di-, or tri-heteroatomic rings, and so on.

In connection with the various carbon rings it has been explained on p. 356 that the five- and six-membered types are the most stable. The same generalisation holds true for heterocyclic rings. Heterocyclic compounds containing three- and four-membered rings are relatively unstable, as is shown by the fact that they are difficult to form and readily break up again. Those containing five- and six-membered rings, on the other hand, are usually distinguished by comparatively high stability.

It should also be noted that the number of heterocyclic systems is increased still further by the existence of condensed polynuclear types. Just as naphthalene is composed of two benzene nuclei, and phenanthrene of a benzene and a naphthalene nucleus, so in the same manner benzene, naphthalene and other rings may condense with heterocyclic systems. A complicated example of this kind has already been met with in

indanthrene (p. 561), and numerous others will be found in connection with quinoline, indole and their derivatives.

Special importance attaches to those compounds in which a five- or six-membered ring containing nitrogen is present. This class includes the vegetable alkaloids and antipyrin, of great value in medicine, and dye-stuffs such as indigo. Compounds derived from these systems will therefore be treated in greater detail. Five-membered rings containing two or more atoms of nitrogen are frequently named with the ending *azole* (pyrazole, triazole, tetrazole) and six-membered rings with the ending *azine* (pyrazine, triazine, tetrazine).

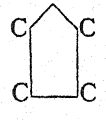
I

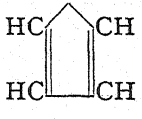
Pyrrole, Furane and Thiophene Groups

The heterocyclic compounds pyrrole, furane and thiophene (see also pp. 254 and 257), which stand in close relationship to each other, will be described first.

I.—PYRROLE GROUP[1]

Among five-membered ring systems containing nitrogen the pyrrole group stands out prominently. Included under this heading are all those chemical compounds, the molecules of which contain a ring built up of four carbon atoms and a nitrogen atom (I).

I. 

II. 

The presence of this ring has been established in a series of important vegetable bases, which were originally regarded solely as derivatives of the six-membered ring compound pyridine; viz., nicotine, hygrine, cuskhygrine, atropine, hyoscyamine, cocaine, tropacocaine and others. Further, E. Fischer obtained pyrrolidine-2-carboxylic acid as a hydrolytic product of various proteins; and other investigators, including Willstätter, proved that hæmoglobin and chlorophyll are pyrrole derivatives, thus revealing an interesting connection between the colouring matter of blood and leaves.

The above examples provide sufficient illustration of the importance of pyrrole derivatives.

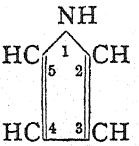
Pyrrole itself, the parent substance of this class, was first discovered in coal tar and bone tar, and is also present among the distillation products

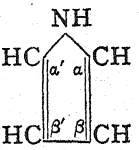
[1] A detailed description of these compounds will be found in a monograph by J. Schmidt, *Die Chemie des Pyrrols und seiner Derivate* (Enke, Stuttgart, 1904).

of bituminous shale. Baeyer was the first to advance the formula (II) now generally accepted for pyrrole.

The structural resemblance between pyrrole compounds and those of furane and thiophene has been clearly demonstrated by the work of L. Knorr and Paal, on the formation of these compounds from γ-diketones or their enolic modifications. This is described more fully below.

Nomenclature of Pyrrole Derivatives.—The position of substituents in the pyrrole nucleus is usually indicated by the numbers 1 to 5, as in formula III.

III. 

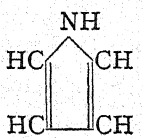
IV. 

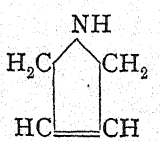
Another system makes use of the letters α, β, as in IV. Since positions α and α′ are equivalent, and also positions β and β′, it is often convenient to distinguish monosubstitution products as α- or β-compounds respectively. Derivatives containing a substituent attached to nitrogen are frequently described as N-compounds.

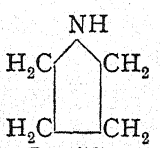
From the above it is seen that each C-monosubstitution product of pyrrole can exist in two isomerides, as an α- or β-derivative. Each C-disubstitution product can occur in four modifications, viz., as an αα′-αβ-, αβ′- or ββ′-derivative.

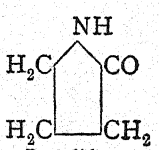
Dihydro-pyrroles are known as **pyrrolines,** and the completely reduced tetrahydro-pyrroles as **pyrrolidines.**

Keto-pyrrolines are termed **pyrrolones,** and keto-pyrrolidines are described as **pyrrolidones.** Distinctions are also drawn between various pyrrolones and pyrrolidones, according to the position and number of keto-groups in the molecule. The term "pyrrolidone" is commonly used to describe 2-keto-pyrrolidine. Substances derived from it can be described either as 2-keto-pyrrolidine or as α-pyrrolidone derivatives, and may be regarded as lactams of γ-amino-acids. The imides of the succinic acid group, of which succinimide itself is the simplest representative, are αα′- or 2 : 5-diketo-pyrrolidines.


Pyrrole


Pyrroline

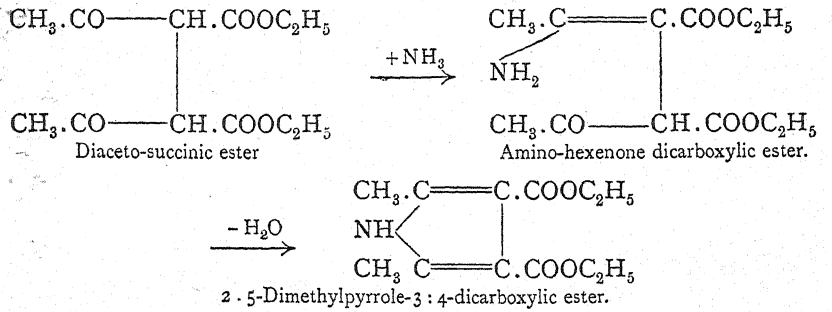

Pyrrolidine


Pyrrolidone.

Methods of Forming Pyrrole and Reduced Pyrrole Derivatives

1. The 1 : 4-diketones, when treated with ammonia or primary amines, are transformed with great ease into pyrrole derivatives. This synthesis is effected with equal readiness when the reagents are dissolved in glacial

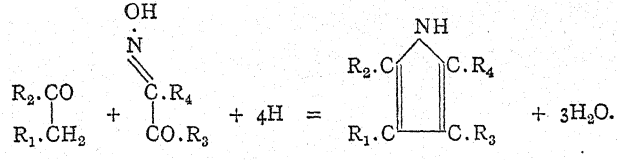
acetic acid, water or ether, and appears to depend on the intermediate formation of amino-ketones (*Knorr*).[1]



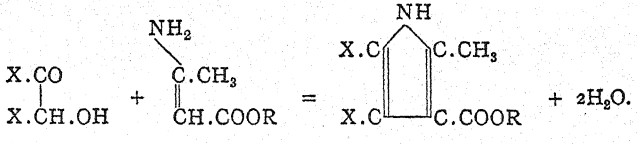
2 . 5-Dimethylpyrrole-3 : 4-dicarboxylic ester.

This reaction has proved of service in the preparation of a great number of pyrrole derivatives. Any γ-diketo-compound of the general formula $R.CO.CH_2.CH_2.CO.R$ may be employed, and the place of ammonia may be taken by primary amines, amino-acids,[2] hydroxylamine or phenyl hydrazine.

2. A second synthesis of pyrrole is also due to L. Knorr, who succeeded in preparing 2 : 4-dimethyl-pyrrole-3 : 5-dicarboxylic ester by reducing an equimolecular mixture of iso-nitroso-acetoacetic ester and acetoacetic ester by means of zinc dust and glacial acetic acid.[3] In a similar manner other pyrrole derivatives were prepared by reducing mixtures of esters of β-ketonic acids and their isonitroso-compounds.



3. In certain cases the reduction of a mixture of an amino-acid ester (*e.g.* amino-crotonic ester) with a 1 : 2-diketone also leads to the formation of derivatives of pyrrole.[4] Reduction may be dispensed with altogether if the diketone is replaced by a 1 : 2-keto-alcohol of the type of benzoin, *e.g.*,

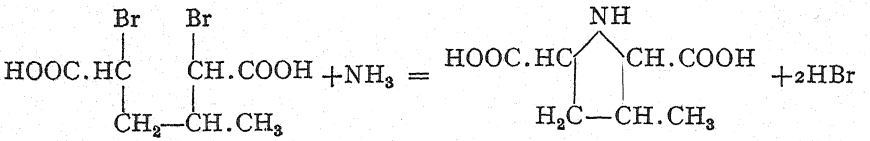


4. A method first used by Hantzsch is to treat β-ketonic esters with chloro-acetone and ammonia, when pyrrole carboxylic esters are formed.[5]

5. Willstätter[6] has shown that the action of ammonia or alkyl amines

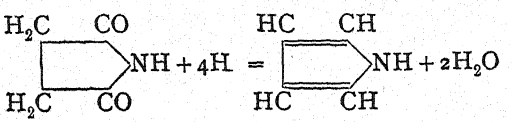
[1] L. Knorr and Rabe, *Ber.*, 1902, **35**, 3801. W. Borsche and Fels, *Ber.*, 1906, **39**, 3877. Since many pyrrole derivatives give a red coloration with a pine splint moistened with hydrochloric acid, the above method of preparing pyrroles may be used as a test for 1 : 4-diketones (*cf.* p. 257). [2] J. Schmidt and Scholl, *Ber.*, 1907, **40**, 3002. [3] L. Knorr, *Ann.*, 1886, **236**, 296. *Ber.*, 1902, **35**, 2998. Piloty, *Ber.*, 1910, **43**, 489. [4] F. Feist, *Ber.*, 1902, **35**, 1558. [5] A. Hantzsch, *Ber.*, 1890, **23**, 1474. *Cf.* also Korschun, *Ber.*, 1905, **38**, 1125. [6] *Ber.*, 1899, **32**, 1290; 1900, **33**, 1160; 1901, **34**, 1818; 1902, **35**, 620, 2065. *Ann.*, 1903, **326**, 91.

on 1 : 4-dibromo-acids of the aliphatic series readily yields carboxylic acids of pyrrolidine.



In a similar manner pyrrolidine derivatives can be obtained by the interaction of primary amines and 1 : 4-dibromo-derivatives of hydrocarbons.

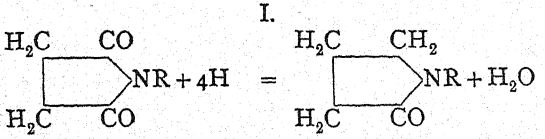
6. Another method of general applicability is based on the reduction of succinimide to pyrrole by means of zinc dust and acetic acid, or hydrogen and heated platinum sponge (*Bell* and *Bernthsen*).



In the same manner substituted pyrroles are formed by the reduction of a variety of acid imides and lactams (which may also be regarded as keto-derivatives of hydrogenated pyrroles).

Different results are obtained by reducing succinimide and its substitution derivatives by electrolytic means [1] (*Tafel*). In this case the corresponding pyrrolidone is formed (formula I), together with very small amounts of pyrrolidine.

I.

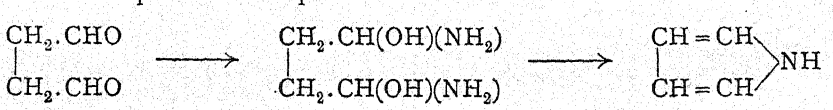


Since succinimides are readily prepared in quantity,[2] this process also renders the pyrrolidones easy of access.

7. On being heated with phosphorus pentachloride, succinimide and the imide of dichloro-maleic acid readily yield chlorinated products, which on reduction give tetrachloro-pyrrole. By way of the tetra-iodo compound the latter may be converted into pyrrole.

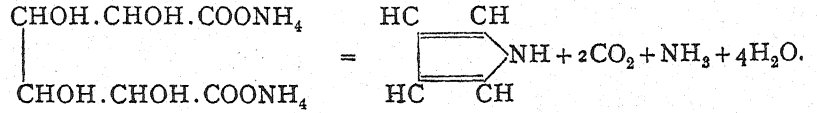
Pyrrole itself is also obtained :

8. By the condensation of succindialdehyde with ammonia [3] ; this is the simplest case of the reaction given under method 1, p. 608. An addition compound is first produced.



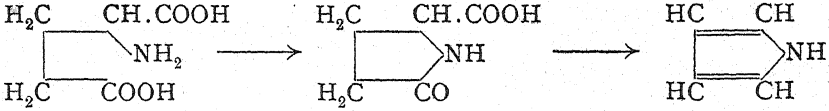
[1] Tafel, *Z. phys. Ch.*, 1906, **54**, 433. B. Emmert, *Ber.*, 1907, **40**, 912. [2] Compare Koller, *Ber.*, 1904, **37**, 1598. [3] Harries, *Ber.*, 1901, **34**, 1488 ; 1902, **35**, 1179.

9. From the ammonium salt of saccharic or mucic acid by distillation, or better by heating with glycerol to 200°.[1]



The use of substituted mucic acids leads to the formation of substituted pyrroles.[2]

10. In a similar manner pyrrole has been obtained from glutamic acid and its calcium salt.



Glutamic acid — Pyroglutamic acid

11. Pyrrole is also formed by leading a mixture of acetylene and ammonia through a tube heated to dull redness.

$$2C_2H_2+NH_3 = C_4H_5N+H_2$$

This reaction explains the occurrence of pyrrole in tar.

1. Compounds of the Pyrrole Series

Pyrrole and its General Properties

Pyrrole, C_4H_4NH. The occurrence (p. 607) and formation (p. 609) of pyrrole have already been treated from the general standpoint.

The *preparation of pyrrole* is best effected from bone tar. This is fractionated several times, freed from strongly basic substances by shaking with dilute acid, and again fractionated. Pyrrole distils over in the fraction boiling between 98° and 150°, and may be purified by conversion into the solid potassium compound.

Pyrrole is a colourless liquid which turns brown in air and smells somewhat like chloroform. It boils at 130° to 131° under 761 mm.; sp. gr. 0·9752 at 12·5°. It dissolves sparingly in water but is readily soluble in alcohol and ether. It is insoluble in aqueous alkalis and only dissolves slowly in acids. On long standing or warming in acid solution a red flocculent precipitate of a substance known as *pyrrole red* separates.

In pyrrole vapour a pine splint moistened with hydrochloric acid is coloured a pale red, which rapidly changes to an intense carmine red. This reaction is employed as a test for pyrrole (see p. 258).

In the presence of dilute acids pyrrole readily unites with a number of compounds containing the group —CO.CO— (such as phenyl glyoxalic acid, benzil, phenanthraquinone, and alloxan) with the formation of dye-stuffs.

Salt Formation with Pyrrole.—Pyrrole is a very weak base which dissolves slowly in dilute acids. With strong acids it is rapidly resinified.

[1] E. Khotinsky *Ber.*, 1909, **42**, 2506. [2] For the mechanism of this reaction see Pictet and Steinmann, *C.*, 1902, **I**, 1297.

Even from solutions in dilute acids it is only possible to isolate definite simple salts in a few cases, and resinification readily takes place. This action of acids on pyrrole is probably due to polymerisation (see below).

Pyrrole combines with picric acid to give a very unstable picrate. With certain metallic salts [1] it yields double compounds.

Salt formation can only be established definitely with derivatives of pyrrole which are stable towards strong acids. Chief among these are derivatives of dimethyl pyrrole containing acetyl or esterified carboxylic acid groups. The negative radicals make the ring more resistant, and at the same time the methyl groups increase the basic properties. In its power of forming salts, pyrrole may be compared to diphenylamine.

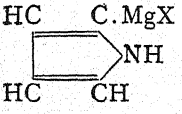
Pyrroles are aromatic in character and possess points in common with both phenols and aromatic amines, as may readily be seen from their reactions.

The analogy with phenols is shown by the similarity in behaviour of the :NH group in pyrrole with that of the phenolic hydroxyl group. Potassium, for example, reacts with pyrrole with evolution of hydrogen and formation of a solid **potassium compound**, C_4H_4NK. Pyrroles, like phenols, readily couple up with diazonium salts to give azo-compounds. In this case the azo-group assumes an α-position, or if both of these are occupied, a β-position. Thus pyrrole and benzene diazonium chloride yield **pyrrole-azobenzene**, $C_6H_5.N:N.C_4H_3:NH$, and **pyrrole disazobenzene**, $C_6H_5.N:N.(C_4H_2:NH).N:N.C_6H_5$, in which the azo-groups are in the α-positions. The analogy with phenols is also borne out in the behaviour of pyrroles towards nitrous and nitric acids. In particular, the nitroso-pyrroles exhibit tautomeric phenomena similar to those shown by the nitroso-phenols (p. 435). Nitroso-pyrrole itself is a very unstable substance and can only be obtained in the form of its sodium compound, $C_4H_3(:N.ONa)N$.

Pyrrole, like phenol and aniline, is readily substituted by halogens, all of the four methine hydrogen atoms being replaceable. The most important halogen derivative is tetra-iodopyrrole, which is described later.

The similarity of pyrrole to aniline is specially evident in its behaviour on alkylation (see below).

Organo-magnesium halides react with pyrrole to form magnesium pyrrole compounds of the type [2]

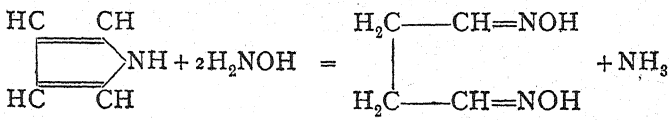


These are useful for the synthesis of pyrrole derivatives having side chains in the α-position. With carbon dioxide, for example, they give pyrrole-α-carboxylic acids.

[1] For a double compound of pyrrole with nickelous ammonium cyanide see Hofmann and Arnoldi, *Ber.*, 1906, **39**, 341. [2] B. Oddo, *Gazz. chim. ital.*, 1910, **39**, I, 649.

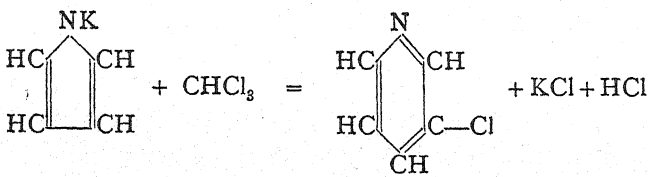
Opening of the Pyrrole Ring by Means of Hydroxylamine

It has been shown by Ciamician that when hydroxylamine reacts with pyrrole the ring is opened and succindialdoxime formed. This reaction is the reverse of the synthesis quoted on p. 610, and appears to be a general one for pyrrole derivatives.



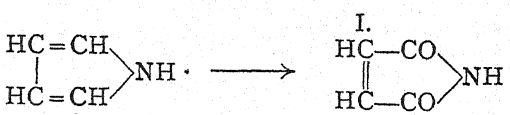
Transformation of the Pyrrole Ring into the Pyridine Ring

When pyrrole or potassium pyrrole is heated with sodium ethoxide and chloroform there is formed *β-chloro-pyridine*.[1] With methylene iodide, pyridine itself is obtained.



This is a general reaction for pyrrole, and is also given by its homologues [2] and the indoles (p. 630).

Oxidation with chromic acid mixture converts pyrrole into the imide of maleic acid (I),



In a similar manner substituted pyrroles, particularly the chloro- and bromo-compounds, are oxidised to substituted maleic derivatives.

This oxidation is a valuable means of determining the orientation of substituents in the pyrrole nucleus and also for detecting the presence of a pyrrole ring in substances of unknown constitution. For example, the pyrrole nature of hæmatin was demonstrated by oxidising the latter to a compound $C_8H_9O_4N$, which proved to be a substituted imide of maleic acid.

Tripyrrole, $(C_4H_5N)_3$, is formed under certain conditions [3] from pyrrole in the presence of hydrochloric acid. When heated to 300°, tripyrrole decomposes into ammonia, pyrrole and indole.[4]

Other polymers obtained from alkyl pyrroles break up in a similar manner, and the process therefore represents *a passage from the pyrrole to the indole series*.

[1] Ciamician and Dennstedt, *Ber.*, 1881, **15**, 1172. Ciamician and Silber, *Ber.*, 1884, **18**, 724. *Cf.* also Plancher and Carrasco, *C.* 1905, **I**, 1155. [2] Bocchi, *Gazz. chim. ital.*, 1900, **30**, **I**, 89. Ciamician, *Ber.*, 1904, **37**, 4231 [3] Dennstedt and Zimmermann, *Ber.*, 1888, **21**, 1478. [4] Dennstedt and Voigtländer, *Ber.*, 1894, **27**, 479.

N-SUBSTITUTED PYRROLES[1]

Potassium pyrrole, C_4H_4NK, is one of the most important derivatives of this type and has been repeatedly mentioned in the foregoing pages. It is formed together with hydrogen when potassium is dissolved in pyrrole, and also on boiling pyrrole with solid caustic potash. A sodium compound cannot be obtained by these methods.

The potassium compound is the starting material in the preparation of a number of N-derivatives of pyrrole, since it reacts readily with various halogen compounds, *e.g.*,

$$C_4H_4NK + I.CH_3 = C_4H_4N.CH_3 + KI$$

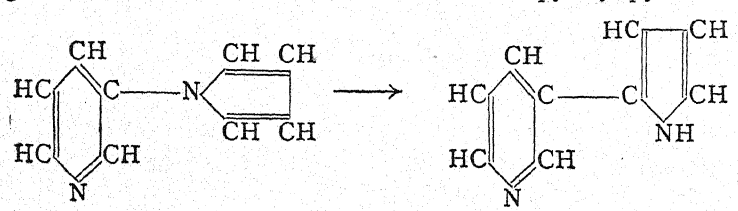
N-Alkyl-pyrroles are also produced by the above pyrrole syntheses by using alkyl amines in place of ammonia. The N-alkyl-pyrroles resemble pyrrole in having feebly basic properties. They do not unite with alkyl iodides and are less reactive than pyrrole.

Wandering of Groups from Nitrogen to Carbon

A point of special interest is that N-derivatives of pyrrole are transformed under the influence of heat into C-derivatives, in the same way as alkylated anilines are converted into homologues of aniline (p. 390).

$$C_4H_4 : N.CH_3 \longrightarrow H_3C.C_4H_3 : NH$$

Pictet and Crepieux,[2] for example, by distilling N-pyridyl-pyrrole through a tube at low red heat converted it into C-pyridyl-pyrrole.



This conversion formed one of the stages of Pictet's synthesis of nicotine.

The N-alkyl-pyrroles have lower melting- and boiling-points than the corresponding C-derivatives.

C-SUBSTITUTED PYRROLES

Among the *halogen derivatives* of pyrrole the most important is tetra-iodopyrrole or **iodole**, $C_4I_4.NH$. It was first prepared by the action of an ethereal solution of iodine on potassium pyrrole (Ciamician and Dennstedt). Later, it was discovered that it could be obtained from

[1] The replaceability of the imide hydrogen atom and the phenolic nature of the pyrroles is supposed to be due to the acidic character of the two C=C groups present in the molecule. Marckwald, *Ann.*, 1894, **274**, 10. *Ber.*, 1895, **28**, 1501. Erlenmeyer, jun., *J. pr. Ch.*, 1900, **62**, 145. [2] *Ber.*, 1895, **28**, 1905.

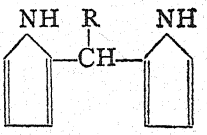
pyrrole, potassium hydroxide and iodine, and also directly from pyrrole and iodine in the presence of indifferent solvents. It has been employed therapeutically in the treatment of wounds in place of iodoform, over which it possesses the advantage of being odourless and less poisonous, although milder in action. It forms shining, yellowish-brown leaflets, which on being heated decompose between 140° and 150°, without melting. When reduced with potassium hydrate and zinc dust, tetra-iodopyrrole is converted into pyrrole. With nitrous or nitric acids it yields nitro-derivatives.

Homologues of Pyrrole.—C-Alkyl-pyrroles are present with pyrrole in bone oil. Their occurrence thus corresponds exactly to that of toluene and the xylenes in coal tar. They may be obtained synthetically by reactions already described in the previous pages, and are of interest in connection with the structure of hæmoglobin and chlorophyll.

Pyrryl magnesium bromide, which is formed with evolution of ethane by the action of magnesium on pyrrole and ethyl bromide in ethereal solution, can also be used in the preparation of alkyl-pyrroles. On interaction with allyl iodide, for example, this compound yields *α-allyl-* and *αα'-diallyl-pyrrole*.[1] By treatment with sodium alcoholates it is possible to introduce methyl and ethyl groups into substituted pyrroles.[2]

C-Alkyl-pyrroles possess the same chemical character as pyrrole itself and give the same colour reactions. In air they change more rapidly than pyrrole, but although resinified with acids are somewhat more stable in this respect than the parent compound.

Pyrrole derivatives with a methyl group in the α-position, and containing at least one unsubstituted nuclear hydrogen atom, have been shown to undergo condensation with aromatic aldehydes.[3] The aldehydes, however, do not attach themselves to the α-methyl group, as is the case with α-substituted pyridine derivatives (see index), nor does the imino-group enter into reaction. Two nuclear hydrogen atoms from two pyrrole molecules are eliminated with the aldehydic oxygen atom in the form of water, and the residues unite to give dipyrryl-aryl-methane derivatives of the general formula



in which the coupling may take place in the α- or β- position of pyrrole.

Pyrrole-2-aldehyde,[4] $C_4H_3(CH:O)NH$, is formed by the interaction of pyrrole and chloroform in the presence of aqueous potassium hydroxide, thus providing a further illustration of the similarity between pyrrole and the phenols (see p. 612). It crystallises

$$C_4H_5N+CHCl_3+3KOH = C_4H_4N(CHO)+3KCl+2H_2O$$

from cooled petroleum ether in colourless odourless prisms, m.p. 45°, and shows no resemblance to benzaldehyde.

[1] K. Hess, *Ber.*, 1913, **46**, 3125. [2] H. Fischer and Bartholomäus, *Zeit. physiol. Ch.*, 1912, **80**, 6. [3] F. Feist, *Ber.*, 1902, **35**, 1647. [4] E. Bamberger and Djierdjian, *Ber.*, 1900, **33**, 536.

Other representatives of this difficultly accessible class have been prepared by H. Fischer, the aldehyde group being introduced into the pyrrole nucleus by Gattermann's method, using anhydrous hydrogen cyanide and dry hydrogen chloride in absolute ethereal solution.

Pyrrole Carboxylic Acids.—A large proportion of the pyrrole derivatives known at present are carboxylic acids. The simple pyrrole carboxylic acids resemble phenol carboxylic acids and are formed by similar reactions, *e.g.* :—

1. By the oxidation of homologues of pyrrole by fusion with potash.
2. By treating potassium pyrroles with carbon dioxide,

$$C_4H_4NK + CO_2 = C_4H_3(COOK)NH$$

3. From pyrroles by interaction with carbon tetrachloride and alcoholic potash.

Esters of homologous pyrrole carboxylic acids can be obtained according to the methods given on p. 608. When heated, the carboxylic acids readily part with carbon dioxide and yield the corresponding pyrrole.

Since pyrrolidine-α-carboxylic acid has been identified as a disruption product of proteins,[1] and other pyrrolidine carboxylic acids have been discovered in tropinic acid and hygrinic acid, which are degradation products of alkaloids, a number of attempts have been made to prepare these acids by hydrogenating the corresponding pyrrole carboxylic acids or esters. So far, however, no satisfactory method of effecting this change has been discovered.

2. Hydropyrrole Derivatives

Hydropyrrole derivatives (see Pyrroline and Pyrrolidine, p. 608) are obtained partly by direct hydrogenation of pyrrole derivatives, partly by the degradation of alkaloids, and partly by synthesis from aliphatic compounds. In addition, certain tetra-hydro-pyrrole bases may be prepared from piperidines by a series of reactions to be described later, which involve the transformation of a six- into a five-membered ring. The reduction of pyrrole compounds to di- and especially to tetra-hydro-derivatives offers considerable experimental difficulty; in this respect these compounds differ from the pyridine group.

Addition of hydrogen brings about a decided change in chemical nature. Whereas pyrrole itself is quite a weak base, pyrroline and to a still higher degree pyrrolidine possess the strong basic properties of the secondary aliphatic amines. This is the usual consequence of hydrogenating an aromatic system, as has already been seen in the case of the naphthylamines and will be observed again in the pyridine group.

Pyrroline is a very volatile colourless liquid, which boils at 90° (748 mm.) and fumes in air. It readily abstracts moisture from the air and is therefore difficult to obtain free from traces of water.

[1] E. Fischer, *Z. physiol. Ch.*, 1901, **33**, 151, 412.

THE PYRROLIDINES

Pyrrolidine and its derivatives present a striking resemblance to the corresponding compounds of the piperidine series. This similarity extends even to physical properties and is best illustrated by comparison with the analogy existing between compounds of the pentamethylene and hexamethylene groups.

The discovery of pyrrolidine in 1885 was followed immediately by the recognition of its resemblance to piperidine and its description as a lower nuclear homologue of the latter (*Ciamician*).

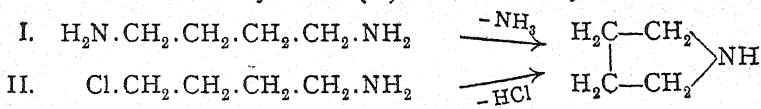
The term nuclear or **ring homology,** which was originally used only to describe the relationship of the free parent bases, can in the state of our present knowledge be extended compound by compound to the corresponding members of the pyrrolidine and piperidine series. In this manner the similarity is found to hold true for all the more important types of derivatives.

Pyrrolidine, *tetrahydro-pyrrole, tetramethylene-imine,* C_4H_8NH, may be obtained by the following methods :—

1. It was first prepared [1] by heating pyrrole with hydriodic acid and phosphonium iodide at 240° to 250°. Obviously the less hydrogenated compound pyrroline must be formed as an intermediate product, and this can also be used as starting material.

2. By the reduction of ethylene cyanide Ladenburg obtained pyrrolidine together with tetramethylene diamine (I). It is also produced by distilling the hydrochloride of tetramethylene diamine.

3. A similar mode of preparation was discovered by Gabriel [2] in the interaction of δ-chloro-butylamine (II) and sodium hydroxide.

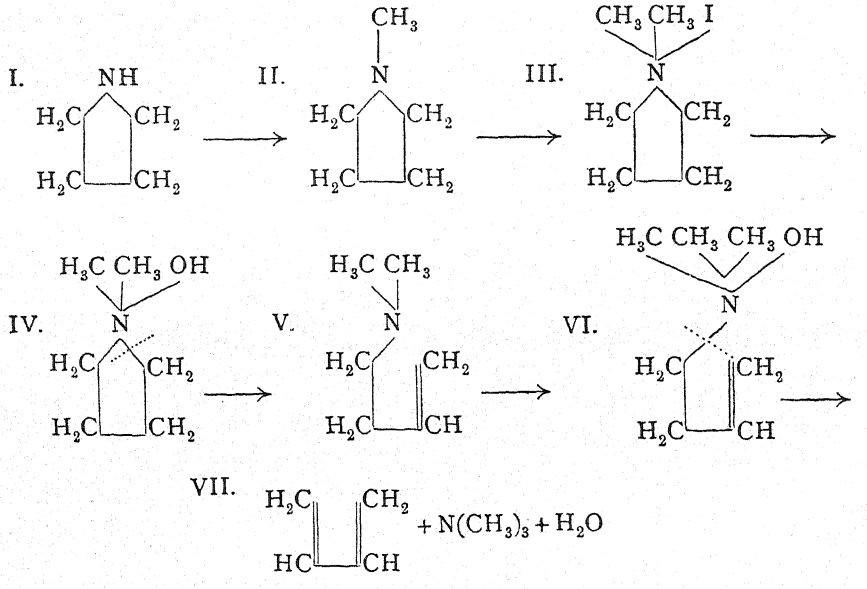


Despite the variety of preparative methods available pyrrolidine is a difficultly accessible compound. It is a strongly alkaline liquid of boiling-point 86° to 88° ; it is miscible with water and possesses a pungent ammoniacal smell recalling that of piperidine. In general it shows great similarity to piperidine.

Behaviour of Pyrrolidine on Exhaustive Methylation.—If dimethyl-pyrrolidinium iodide (III) be heated with caustic potash a decomposition ensues resembling that described below under dimethyl-piperidinium hydroxide. Under these conditions the ring opens [3] with formation of an unsaturated aliphatic base, Δ^3-butenyl-dimethylamine (V), (incorrectly called dimethyl pyrrolidine). The methiodide of this base, on distillation

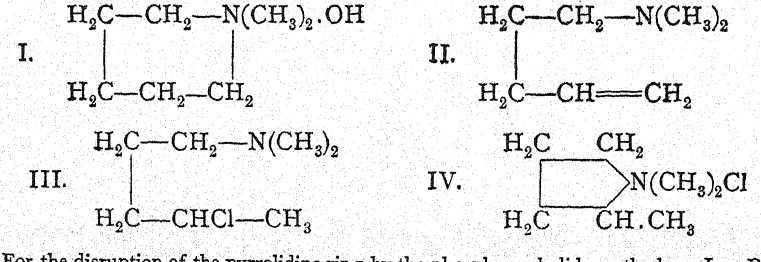
[1] Ciamician and Magnaghi, *Ber.*, 1885, **18**, 2079. More recently the reduction has been effected by means of nickel as catalyst by the method of Sabatier and Senderens (Padoa, *C.*, 1906, **I**, 1436). [2] *Ber.*, 1891, **24**, 3233. *Cf.* also Schlinck, *Ber.*, 1899, **32**, 947. [3] Detailed information as to the behaviour of the different cyclic bases on "exhaustive methylation" will be found in a monograph by J. Schmidt, *Ueber die Halogenalkylate und quaternären Ammoniumbasen* (Enke, Stuttgart, 1899).

with alkali, yields trimethylamine and an unsaturated aliphatic hydrocarbon known as divinyl (VII). The exhaustive methylation of pyrrolidine may be represented in the following stages [1] :—



Homologues of Pyrrolidine.—The preparative methods described under pyrrolidine are also available for the formation of its homologues (see p. 617) In addition, a reaction has been discovered by Merling,[2] by means of which *the six-membered piperidine ring can be converted into the five-membered ring of pyrrolidine.*

Piperidine, or pentamethylene-imine, unites with methyl iodide to form dimethyl-piperidinium iodide, the hydroxide of which (I) on distillation gives an open-chain compound (II) known as Δ^4-pentenyl-dimethylamine (sometimes incorrectly called dimethyl-piperidine). The addition product (III) formed by the latter with hydrochloric acid easily isomerises into the methochloride of 1 : 2-dimethyl-pyrrolidine (IV), which on stronger heating breaks up into methyl chloride and 1 : 2-dimethyl-pyrrolidine.



[1] For the disruption of the pyrrolidine ring by the phosphorus halide method see J. v. Braun, *Ber.*, 1906, **39**, 4119. Investigation of the disruption by means of cyanogen bromide has led to the unexpected result that the pyrrolidine ring is much more readily opened than the piperidine ring, J. v. Braun, *Ber.*, 1911, **44**, 1152. [2] *Ann.*, 1891, **264**, 310; 1894, **278**, 1.

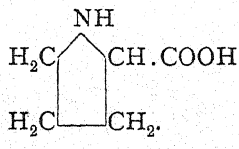
Just as pyrrolidine on exhaustive methylation gives the unsaturated hydrocarbon divinyl, $CH_2:CH.CH:CH_2$ (see p. 618), 3-methyl-pyrrolidine gives β-methyl-divinyl, $CH_2:CH.C(CH_3):CH_2$, which is more commonly known as isoprene.[1]

PYRROLIDINE CARBOXYLIC ACIDS

Certain important degradation products of the *coca* and *atropa* alkaloids have been identified as carboxylic acids of pyrrolidine, viz., hygrinic acid and tropinic acid. Further, it was shown by E. Fischer that pyrrolidine-2-carboxylic acid occurs as a hydrolysis product of casein, egg albumin, blood fibrin and other albuminous substances when they are treated with hydrochloric acid.

As a result of the above discoveries the pyrrolidine carboxylic acids, which had previously been little examined, were investigated in greater detail. For general methods of synthesising these compounds reference should be made to p. 616. The application of the methods to special cases is described below.

Pyrrolidine-2-carboxylic acid, *α-pyrrolidine carboxylic acid, proline,* was first isolated in an optically impure *l*-form by E. Fischer, from the mixture obtained by hydrolysing casein with hydrochloric acid. It has since been obtained from a number of other proteins.[2]



Hence it must be assumed that pyrrolidine-2-carboxylic acid is a primary product of the hydrolysis of proteins, and that it is an important unit of the protein molecule.

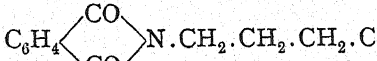
Syntheses of Pyrrolidine-2-carboxylic Acid.—1. The synthesis of Willstätter and Ettlinger[3] is an adaptation of the general procedure described under 5, p. 609, and is carried out as follows :—

Molecular quantities of trimethylene bromide and sodio-malonic ester interact under certain conditions to give bromo-propyl-malonic ester, according to the equation :

$$CHNa(COOC_2H_5)_2+CH_2Br.CH_2.CH_2Br = NaBr+CH_2Br.CH_2.CH_2.CH(COOC_2H_5)_2$$

This, when treated with bromine, yields $\alpha\delta$-dibromo-propyl-malonic ester, which can be condensed with ammonia to form the diamide of pyrrolidine-2-dicarboxylic acid. On heating with hydrochloric acid the latter is smoothly converted into pyrrolidine-2-carboxylic acid.

2. Fischer has prepared the compound in a similar manner by the interaction of ammonia and phthalimido-propyl-bromomalonic ester,



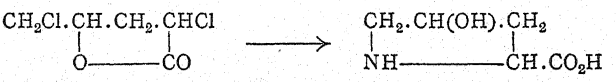
[1] W. Euler, *C.*, 1898, I, 247. [2] E. Fischer and co-workers, *Z. physiol. Ch.*, 1901, **33**, 151, 412; **35**, 80, 227; **36**, 268, 462; **39**, 81; **40**, 215. Ssalaskin and Kowalewsky, *ibid.*, 1903, **38**, 567. Kossel, *ibid.*, 1904, **40**, 311. Abderhalden, *ibid.*, 1904, **41**, 55; **44**, 17, 276; **46**, 24, 31. C. Neuberg, *C.*, 1904, **II**, 1576. [3] Willstätter and Ettlinger, *Ber.*, 1900, **33**, 1160. *Ann.*, 1903, **326**, 91.

3. According to Putochin [1] proline may be prepared by the direct action of trimethylene bromide on amino-malonic ester, $NH_2.CH(COOC_2H_5)_2$. Naturally these syntheses yield the acid in the racemic form.

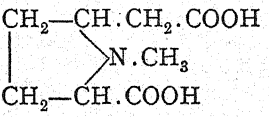
After careful drying, dl-*pyrrolidine-2-carboxylic acid* melts with gas evolution at 205°. In aqueous solution it gives a weakly acid reaction with litmus, and possesses a sweet taste. For the separation and identification of the acid the *copper salt* [2] is of service, and has frequently been used by Fischer for identifying the compound obtained from proteins. If the acid be saturated with precipitated copper hydroxide a dark blue solution is obtained from which the copper salt ($2H_2O$) deposits in deep blue four-sided plates. The salt dissolves readily in hot water, but only sparingly in the cold. It is slightly soluble in alcohol and insoluble in chloroform.

l-*Pyrrolidine-2-carboxylic acid* forms flat needles, melting at 205°. Rotation in aqueous solution $[\alpha]_D^{20} = -71{\cdot}94$ to $-77{\cdot}40°$; in hydrochloric acid solution $[\alpha]_D^{20} = -46{\cdot}53°$; and in alkaline solution $[\alpha]_D^{20} = -83{\cdot}48°$. On being heated for five hours with baryta at 140° to 145°, it is converted into the racemic form.

β′-Hydroxy-pyrrolidine-α-carboxylic acid, *hydroxy-proline,* has been identified by E. Fischer among the hydrolysis products of gelatin and synthesised by Leuchs [3] in its various stereoisomeric forms by the action of ammonia on αδ-dichloro-valerolactone.



Tropinic acid, 1-methyl-pyrrolidine-2-carboxy-5-acetic acid



When tropine and ecgonine (see chapter on Alkaloids) are oxidised with chromic acid [4] they yield dicarboxylic compounds, $C_8H_{13}NO_4$, known as tropinic acids. These differ only in their optical properties, the oxidation product from tropine being inactive, and that from ecgonine dextrorotatory.

The constitution of tropinic acid has been established by Willstätter in the following way:

1. Tropinic acid derived from various sources was submitted to exhaustive methylation, and in every case the same product of composition, $C_5H_6(COOH)_2$, was obtained, which from its behaviour with bromine was shown to be a diolefinic dicarboxylic acid. This acid, on being reduced in alkaline solution with sodium amalgam, gave a partly

[1] N. J. Putochin, *Ber.*, 1923, **56**, 2213. [2] *Ann.*, 1903, **326**, 105. *Ber.*, 1901, **34**, 459. [3] H. Leuchs and Bormann, *Ber.*, 1919, **52**, 2086. [4] C. Liebermann, *Ber.*, 1890, **23**, 2518; 1891, **24**, 606. For the preparation of tropinic acid from tropine and ecgonine compare also Willstätter, *Ber.*, 1895, **28**, 3278 (footnote). *Ber.*, 1898, **31**, 1547.

reduced acid together with a saturated acid identified as normal pimelic acid.[1] These facts taken in conjunction with certain reactions of tropinone (see this) were sufficient to establish the constitution of tropinic acid.

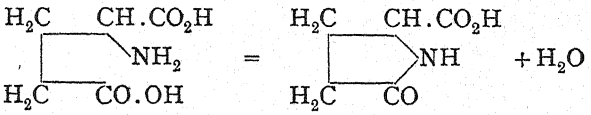
2. By treating tropinic acid (or better, ecgoninic acid) with chromic acid mixture Willstätter obtained methyl-succinimide. The pyrrolidine nucleus of this acid, and therefore of tropine and ecgonine, has thus been isolated in the form of a simple well-known compound.

Racemic tropinic acid is very soluble in water, difficultly soluble in alcohol, and insoluble in benzene and ether. It melts indefinitely with decomposition at about 250°. d-*Tropinic acid*, obtained by the oxidation of either *l*- or *d*-ecgonine, melts at 253°, $[\alpha]_D = +14{\cdot}8°$ in water.

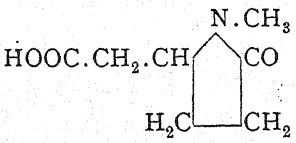
CARBOXYLIC ACIDS OF 2-KETOPYRROLIDINE (α-PYRROLIDONE)

The acids of chief interest in this group are pyrrolidone-5-carboxylic acid, a hydrolysis product of proteins, and ecgoninic acid (1-methyl-pyrrolidone-5-acetic acid) which is an oxidation product of tropine and ecgonine.

Pyrrolidone-5-carboxylic acid, *2-ketopyrrolidine-5-carboxylic acid*, $C_4H_5O(COOH)NH$, was first obtained by heating optically active glutamic acid (α-amino-glutaric acid) at 180° to 190°, and was therefore described under the name of pyroglutamic acid. The same acid has also been obtained by heating protein with baryta at 180°. Subsequently it was prepared from inactive glutamic acid, of which it is the lactam, and investigated in greater detail.[2]



Ecgoninic acid, 1-*methyl-pyrrolidone-5-acetic acid*.



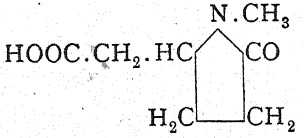
It has already been stated (p. 620) that the oxidation of tropine or ecgonine with chromic acid yields tropinic acid. In addition, Liebermann observed that two modifications of ecgoninic acid were produced as by-products in this reaction: *l*- and *d*-ecgonines were found to give a laevo-rotatory acid, m.p. 117°, while tropine gave an acid of doubtful purity, melting about 90°. Later it was shown by Willstätter [3] that the ecgoninic acid from tropine is the racemic form, whereas that from ecgonine is the *l*-variety.[4] The acids are alike in all important properties, but differ in

[1] *Ber.*, 1898, **31**, 1534. [2] L. Wolff, *Ann.*, 1890, **260**, 124. [3] Willstätter and Bode, *Ber.*, 1901, **34**, 519. [4] The degradation of tropine and ecgonine to ecgoninic acid, in which tropinic acid is probably an intermediate stage, is dealt with in more detail in connection with the vegetable alkaloids.

melting-point (*r*-form melts at 93° to 94°) and to some extent in solubility. The above constitution has been confirmed by Willstätter's synthesis of the racemic acid, which was effected in the following manner :—

Δ^2-*Dihydro-muconic acid*, which has been synthesised from glyoxal and malonic acid, combines with HBr to form β-bromo-adipic acid. In methyl alcoholic or benzene solution this readily reacts with methyl-

I. $HOOC.CH_2.CHBr.CH_2.CH_2.COOH + 2NH_2CH_3$
(β-Bromo-adipic acid)
$= HOOC.CH_2.CH(NH.CH_3).CH_2.CH_2.COOH + NH_2CH_3, HBr$

II. $HOOC.CH_2.CH(NH.CH_3).CH_2.CH_2.COOH = H_2O +$ 

amine to give ecgoninic acid, probably through the intermediate formation of methylamino-adipic acid.

The synthetic product is identical in all respects with that obtained by the oxidation of tropine. This synthesis provided the first direct proof of the existence of a pyrrolidine ring in atropine and cocaine.

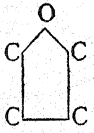
r-*Ecgoninic acid* crystallises in white needles, m.p. 93° to 94°. It is readily soluble in water, alcohol and chloroform, dissolves very sparingly in boiling benzene and is practically insoluble in ether or ligroin. It has no physiological action. The pyrrolidone ring in this compound is so stable that it has not yet been found possible to convert the acid into the open-chain β-methylamino-adipic acid.

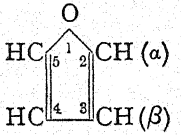
l-*Ecgoninic acid*[1] can be obtained, as mentioned above, from *l*- or *r*-ecgonine. It melts at 117° to 118°, and is less soluble than the *r*-acid.

The *alkaloids of the pyrrolidine group* are treated in a later chapter.

II.—FURANE GROUP

Furane, as indicated on p. 254, is closely related to pyrrole, but is of much less importance than the latter. It contains a ring composed of four carbon atoms and one oxygen atom (I),

I. 

II. 

which may be regarded as a pyrrole ring in which the NH group is replaced by O.

The synthetic formation of furane derivatives by elimination of water from γ-diketo-compounds has already been described (see pp. 254 and 257), and affords a good illustration of the close relationship existing between furane and pyrrole.

[1] Willstätter and co-workers, *Ber.*, 1901, **34**, 522 ; *Ann.*, 1903, **326**, 90.

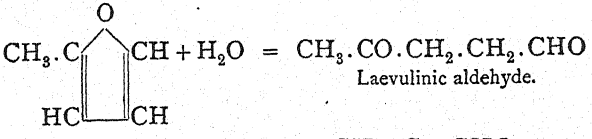
Furane or *furfurane*, C_4H_4O (formula II), can be obtained from mucic acid (*cf.* p. 611). On dry distillation the latter is converted into *pyromucic* or *furane-carboxylic acid*, which when heated in a sealed tube at 270° yields furane.

$$\underset{\text{Mucic acid}}{C_4H_4(OH)_4(COOH)_2} \longrightarrow \underset{\text{Pyromucic acid}}{C_4H_3O(COOH)} \longrightarrow \underset{\text{Furane.}}{C_4H_4O} + CO_2$$

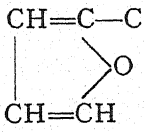
It is a colourless liquid with a peculiar smell resembling that of chloroform. Furane boils at 32° and is insoluble in water. The vapour gives a green coloration to a pine splint moistened with hydrochloric acid.

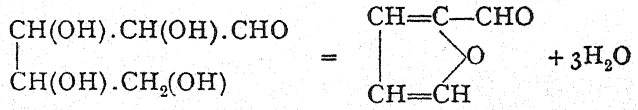
The position of substituents in the furane nucleus is indicated, as in the case of pyrrole, by letters or numbers (formula II).

α-Methyl-furane, sylvane, is contained in the volatile portion of the tarry oil from *Pinus sylvestris*, in which dimethyl-furane and higher methylated products are also present; it can be isolated from the fraction of beech tar creosote [1] boiling between 60° and 70°. It boils at 65° and is a colourless mobile liquid of pleasant ethereal smell. It gives an emerald green coloration to a pine splint moistened with concentrated hydrochloric acid. On hydrolysis with hydrochloric acid [1] it yields laevulinic aldehyde.



Laevulinic aldehyde.

Furaldehyde, *furfural*, *furfurole*,  , has been known for a long time. It is formed by the distillation of bran, wood or various carbohydrates with sulphuric acid, but is best prepared from arabinose or xylose—or from corn-cob gum,[2] which is rich in pentoses—by treatment with moderately concentrated sulphuric acid (see p. 297).



It boils at 162°, and is a colourless oil of pleasant smell.

In its chemical character furfural is aromatic in type and a complete analogue of benzaldehyde. Like all aldehydes it forms an oxime and a hydrazone, and in addition undergoes a series of reactions in which the resemblance to benzaldehyde is clearly visible. Thus with alcoholic potassium cyanide it yields *furoin*, $(C_4H_3O).CHOH.CO.(C_4H_3O)$, an analogue of benzoin; with sodium acetate and acetic anhydride it is converted into *furyl-acrylic acid*, $(C_4H_3O).CH:CH.COOH$ (compare cinnamic acid by *Perkin's* reaction). It also undergoes the *Cannizzaro* reaction to give *furyl alcohol* and *furoic acid*.

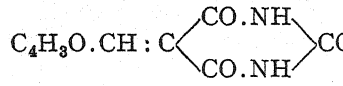
[1] C. Harries, *Ber.*, 1897, **30**, 230. [2] K. P. Monroe, *J. Ind. and Eng. Ch.*, 1921, **13**, 133.

In an attempt to discover some technical use for the large quantities of furfural produced as a by-product in industry, its behaviour towards phenolic compounds has been examined.[1] As in the case of formaldehyde, it is found that condensation takes place, particularly in the presence of suitable catalysts, with the elimination of water and the production of brownish-black substances. These possess the properties of resins, and in most respects resemble the " Bakelites " produced by condensing formaldehyde with phenols (p. 186). Furfural is used in the preparation of artificial resins, dyes and insecticides.

As already mentioned, the conversion of pentoses into furfural is employed in determining the proportion of pentoses or pentosans present in various mixtures. In this connection a number of insoluble derivatives have been found by means of which furfural may be separated from solution, *e.g.* furfural phloroglucide, probably formed according to the equation

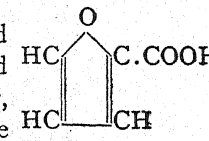
$$C_6H_6O_3+C_5H_4O_2 = C_{11}H_8O_4+H_2O$$

and the condensation product of furfural and barbituric acid, which is a very insoluble powder of the formula



A qualitative test for furfural is the formation of an intensely red dyestuff when it is heated with aniline and hydrochloric acid.

Pyromucic acid, α-furane-carboxylic acid, is formed, as described above, during the dry distillation of mucic acid, and also by the oxidation of furfural. It crystallises in needles, m.p. 134°, which sublime at 100° and dissolve readily in hot water or alcohol.[2]



From the properties of furfural it might be expected that pyromucic acid would behave as an aromatic acid and as the analogue of benzoic acid. This, however, is not the case. The reactions of pyromucic acid give no indication of aromatic character, but rather place it with the unsaturated aliphatic acids. Thus it immediately decolorises an alkaline solution of permanganate of potash, and when exposed to bromine vapour takes up four atoms of bromine. On warming with bromine water it is converted into fumaric acid, and on catalytic hydrogenation it yields *tetrahydro-pyromucic acid* (m.p. 21°, b.p. 131°/14 mm.)

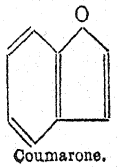
Another acid of this series is *furane*-2 : 4-*dicarboxylic acid*, m.p. 266°. The formation of this substance by heating bromocoumalinic ester with potassium hydroxide is of interest as representing the transformation of a six- into a five-membered ring.[3]

3-*Aminofuranes* can be diazotised and coupled with β-naphthol, but in their other reactions the diazotised amines do not resemble the aromatic derivatives.

[1] E. Beckmann and Dehn, *Ch. Zeit.*, 1919, **I**, 440. [2] *Ann.*, **261**, 379. [3] F. Feist, *Ber.*, 1901, **34**, 1992.

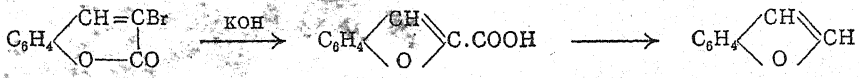
Coumarone or Benzofurane Series

Compounds of this class contain a benzene and a furane nucleus condensed together with two carbon atoms in common. The parent substance of the group, coumarone, thus bears the same relationship to naphthalene as furane to benzene. To furane it is related in the same way as indole (see later) to pyrrole.



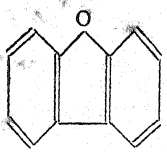
Coumarone.

Coumarone derivatives take their name from their formation by the action of alcoholic potash on α-halogen-substituted coumarins, as a result of which a six-membered ring is converted into a five-membered ring :



α-Bromocoumarin Coumarilic acid Coumarone.

Coumarone can be prepared by other methods [1] in addition to those described above, and is also found together with a number of methyl coumarones in coal tar. It boils at 169° to 170°, and is an extremely stable, indifferent compound. Strong mineral acids bring about resinification and formation of a polymeride known as *paracoumarone*. On leading a mixture of coumarone and benzene (or naphthalene) in the vaporous state through a heated tube, phenanthrene (or chrysene, see p. 580) is formed.

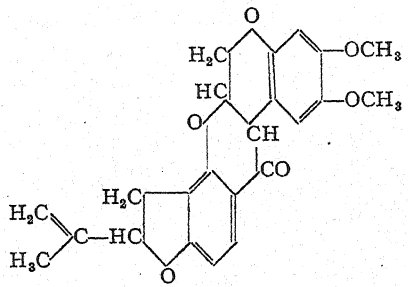


Diphenylene oxide.

With chlorine and bromine coumarone yields dihalogen addition products, which, on being treated with alcoholic potash, give chloro- and bromo-coumarones. Nitro-derivatives are also known. A large number of derivatives containing alkyl groups in the benzene and furane nuclei have been prepared by synthesis.

Diphenylene oxide may be regarded as **dibenzo-furane.** It forms white leaflets, m.p. 81°, b.p. 288°, and is found in coal tar. Synthetically, it may be obtained by various methods, *e.g.* from phenol by distillation with lead oxide.

Rotenone—A number of plant products having the properties of fish poisons and insecticides are derived from coumarone. One of the best known of these is **rotenone,** the active principle of derris root (*derris elliptica*). The weed grows in the Amazon basin and is used by the natives for killing fish in pools. It is not poisonous to humans and large quantities are exported as a cheap and efficient insecticide. According to La Forge [2] and Butenandt [3] rotenone has the following constitution :

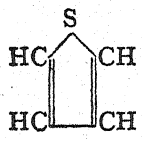


III.—THIOPHENE GROUP

Whereas pyrrole, as already emphasised, shows a strong resemblance to the phenols, thiophene possesses many points in common with benzene. This similarity extends also to derivatives of these compounds.

[1] *Cf.* R. Stoermer, *Ber.*, 1897, **30**, 1700, 1711. *Ann.*, 1900, **312**, 237 ; **313**, 79. P. Karrer and co-workers, *Helv. Chim. Acta*, 1920, **3**, 541 ; 1921, **4**, 718. [2] F. B. La Forge and H. L. Haller, *J. A. C. S.*, 1932, 54, 810. [3] A. Butenandt and W. McCartney, *Ann.*, 1932, **494**, 17

Thiophene is present to about 0·5 per cent. in the benzene obtained from coal tar, in which it was discovered in 1883 by Victor Meyer. In addition it is found in the lower boiling fractions of the tar from brown coal. Homologues of thiophene are present in the benzene homologues prepared from coal tar; thus the two possible (α and β) methyl-thiophenes or **thiotolenes**, $C_4H_3(CH_3)S$, are contained in commercial toluene, and the dimethyl-thiophenes or **thioxenes**, $C_4H_2(CH_3)_2S$, in xylol. This is explained by the fact that corresponding homologues of the benzene and thiophene series possess approximately the same boiling-points. Thiophene and its homologues may be isolated from the above aromatic hydrocarbons by taking advantage of the fact that they are more readily sulphonated than the latter on treatment with concentrated sulphuric acid.



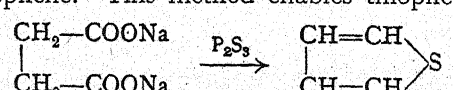
Many bituminous tars and oils, such as crude *ichthyol oil*, consist largely of *thiophene homologues*. Propyl derivatives of thiophene have been isolated in comparatively large proportion from certain shale tar oils.

Synthetically, thiophene derivatives are formed in a similar way to those of pyrrole and furane from γ-diketo-compounds by treatment with phosphorus pentasulphide (see pp. 254 and 257), and also by distilling succinic acid and its homologues with phosphorus pentasulphide.

Thiophene and its derivatives all give the *indophenine reaction, i.e.*, when treated with concentrated sulphuric acid and a little isatin, particularly in the presence of certain oxidising agents such as ferric chloride or nitric acid, a characteristic blue coloration is produced.

Thiophene can be extracted from commercial benzene by repeated shaking with small quantities of concentrated sulphuric acid, and decomposing the sulphonic acid so obtained by heating it strongly with water. This method of separation is by no means an ideal one, since either a certain proportion of benzene is simultaneously sulphonated, or, by using smaller amounts of sulphuric acid, the thiophene is only incompletely removed from benzene.

A better and quantitative method of isolating thiophene from commercial benzene has been developed by O. Dimroth.[1] This consists in heating the mixture to the boiling-point with a solution of mercuric acetate, when thiophene is attacked with the formation of *thiophene-$\alpha\alpha'$-dimercuri-hydroxyacetate*, $HOHg.C_4H_2S.HgOOC.CH_3$. The latter separates out as a solid, whereas the less reactive benzene is not attacked at this temperature. On distilling the mercury compound with moderately concentrated hydrochloric acid it readily decomposes into mercuric chloride and thiophene. This method enables thiophene to be isolated



in the pure state without loss of either thiophene or benzene. Thiophene may be synthesised by passing ethyl sulphide vapour through a red-hot

[1] *Ber.*, 1899, **32**, 759; 1902, **35**, 2035.

tube, and by other pyrogenic reactions. In larger quantities it is obtained by heating sodium succinate with phosphorus trisulphide.

It possesses almost the same smell and boiling-point (84°) as benzene (80·4°), which it also closely resembles in its behaviour towards various reagents. Thus chloro- and bromo-substitution products of thiophene may be prepared by the direct action of the halogens, in the same way as the corresponding benzene derivatives, although the reaction takes place more readily than with benzene. Mono- and dinitro-thiophenes are formed when air saturated with thiophene vapour is led through cooled fuming nitric acid. Mononitro-thiophene melts at 44°, boils at 224°, and has a smell resembling that of nitrobenzene. These nitro-compounds, however, are not reduced with the same ease as the nitro-benzenes, since the majority of reducing agents lead to their complete decomposition. The readiness with which thiophene is sulphonated has been mentioned above.

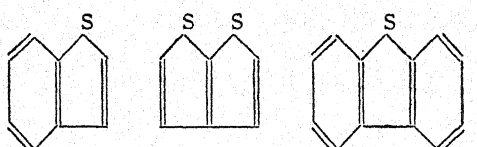
Homologues of thiophene are prepared from γ-diketones or alkyl succinic acids. They may also be obtained from thiophene by reactions analogous to those used in the preparation of benzene homologues from benzene, *e.g.* by Fittig's synthesis from sodium and a mixture of iodo-thiophene and an alkyl iodide, or from thiophene, alkyl bromide and aluminium chloride, and so on.

$$C_4H_3IS+CH_3I+2Na = C_4H_3(CH_3)S+2NaI$$

Thiophene-aldehyde, $C_4H_3(CHO)S$, can be obtained by the action of hydrogen sulphide on chlorinated 1 : 2-diketo-pentamethylene. In its properties it resembles benzaldehyde rather than furfural.

Thiophene carboxylic acids are prepared in a similar manner to those of the benzene series by oxidising derivatives of thiophene, when the side chain is converted into a carboxyl group. The α-acid can also be prepared by the action of sodium on a mixture of iodo-thiophene and chloro-carbonic ester. It resembles benzoic acid and crystallises from hot water in needles, m.p. 126·5°.

Condensed thiophenes and benzo-thiophenes are also known comparable to the corresponding benzene compounds, *e.g.*,



Thionaphthene Thiophthene Diphenylene sulphide.

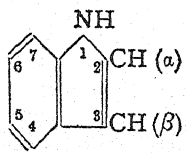
Thionaphthene[1] melts at 31°, and boils at 221°, *i.e.*, at almost the same temperature as naphthalene (218°). It also resembles the latter in smell. The true analogue of naphthalene in this series is **thiophthene,** which is formed by heating citric or tricarballylic acid with phosphorus sulphide, and is an oil of faint smell, b.p. 224° to 226°. **Diphenylene sulphide,** a compound of anthracene type, is produced when diphenyl sulphide is led through a glowing tube. It melts at 97° and boils at 332°.

[1] For a synthesis see Gattermann and Lockhart, *Ber.*, 1893, **26**, 2808.

II

Benzopyrrole or Indole Group

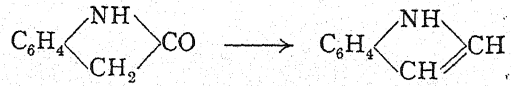
The molecule of indole contains a benzene nucleus condensed with a pyrrole nucleus, as in the annexed formula. As the parent substance of indigo it possesses an outstanding interest. Indole and its derivatives are also important from the chemico-physiological point of view, owing to their occurrence as disruption products of proteins. Four compounds of this group have long been known to be present among the putrefaction products of proteins, namely, indole itself, skatole, skatole-carboxylic acid and tryptophane. A valuable series of investigations on compounds of the indole group was carried out by Baeyer in connection with the constitution and synthesis of indigo. The results obtained have contributed not only to our knowledge of indole derivatives, but also very largely to our progress in general organic chemistry. Thus the theory of ring-formation gained considerably from the study of indole, and the theory of tautomerism from that of isatin. Further, the researches on indigo led to the discovery of a number of new methods which have since been applied with success to other branches of organic chemistry.



Indole, C_8H_7N, is produced in small amounts by the putrefaction of albuminous material, and is present in fæces ; it is also formed by the alkaline hydrolysis of proteins. It occurs in coal tar, and has been isolated from a fraction of tar oil, boiling between 240° and 260°. Indole is also present in jasmine-flower oil (2½ per cent.), in orange blossom and other flowers. The structural formula quoted above was advanced by Baeyer before the compound itself had been discovered.

Indole is obtained by the following reactions :—

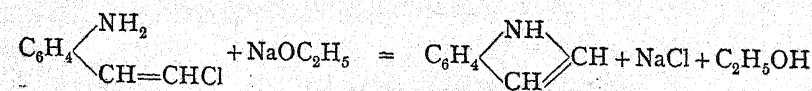
1. From its oxygenated derivatives, such as indigo, oxindole or indoxyl, by reduction. For example, by distilling oxindole with zinc dust.



It was first prepared by the reduction of indigo blue.

2. By leading ethylaniline or other alkyl derivatives of aniline—particularly cumidine—through a red-hot tube.

3. By the condensation of various *o*-substitution products of aniline (or of nitrobenzene, after preliminary reduction) ; *e.g.*, from *o*-amino-chloro-styrole on treatment with sodium ethoxide.



4. From *o*-amino-benzyl cyanide by intramolecular rearrangement in presence of alkalis.[1] In this manner α-amino-indole is first produced, which then parts with ammonia to give indole.

The best preparative method consists in the reduction of indoxylic acid or of indoxyl in alkaline solution.[2]

Indole crystallises in plates, m.p. 52° and b.p. 245° (with partial decomposition). It is volatile in steam, and in the ordinary state possesses an unpleasant fæcal odour. After very careful purification, however, indole may be mixed in suitable dilution with other perfumes, with the surprising result that the odour of fresh flowers is imparted to the mixture. The presence of indole in jasmine-flower oil is therefore a very important factor in producing the specific perfume of jasmine.

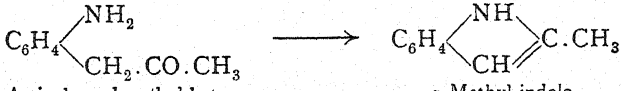
Indole, like pyrrole, possesses weakly basic and at the same time somewhat phenolic properties. Similarly, it is easily resinified with acids, and gives a cherry-red colour to a pine splint moistened with hydrochloric acid.

A large number of substitution products are known, the position of substituents being indicated by the use of α-, β-, N- or figures, as in the formula on p. 628. Positions 1 and 3 are especially reactive. Thus with acetic anhydride at 200° indole yields a mixture of 1-acetyl and 1 : 3-diacetyl indole. With iodine and very dilute alkali 3-iodoindole is obtained. Sodium ethylate and amyl nitrite convert indole into 3-nitroso-indole.

ALKYL AND ARYL SUBSTITUTION PRODUCTS OF INDOLE

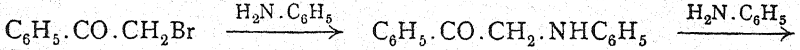
Homologues of indole occur in coal tar, and may be prepared from the higher fraction, b.p. 250° to 275°, of the technical crude indole.[3] They are synthesised by the following methods :—

1. In an analogous manner to the formation of indole itself by the condensation of aromatic *o*-amino-compounds, *e.g.*,

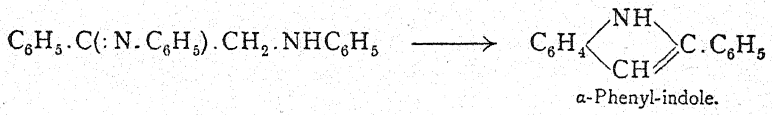


o-Aminobenzyl methyl ketone — α-Methyl-indole.

2. By the action of substituted anilines on anilides of ketones or aldehydes of the general formula $R'.CO.CH(NHC_6H_5).R''$. Anilides



Bromo-acetophenone, Phenacyl bromide — Phenacyl anilide



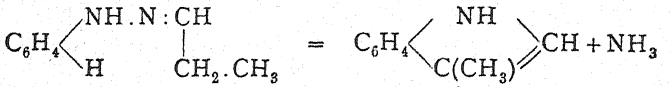
α-Phenyl-indole.

of this type may be prepared from halogen derivatives of ketones and aldehydes, in which halogen is attached to the carbon atom adjacent

[1] R. Pschorr and Hoppe, *Ber.*, 1910, **43**, 2543. [2] Vorländer and Apelt, *Ber.*, 1904, **37**, 1134.
[3] O. Kruber, *Ber.*, 1926, **59**, 2752.

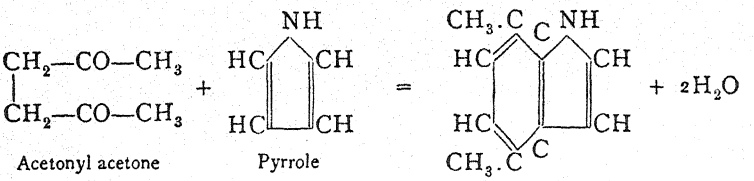
to the carbonyl group, *i.e.*, from compounds containing the group —CO.CHCl—.[1]

3. By heating the phenylhydrazones of certain aldehydes and ketones, or of pyroracemic acid, with zinc chloride (Fischer):



Propaldehyde-phenylhydrazone — β-Methyl-indole.

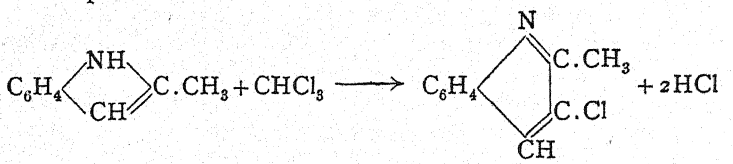
The true homologues of indole, with the substituent in the pyrrole ring, are prepared chiefly by methods 1 and 3. But derivatives with the substituent in the benzene nucleus can also be obtained by these processes if use is made of starting materials substituted in the phenyl group. Thus 4 : 7-dimethyl-indole has been prepared from the *p*-xylyl-hydrazone of pyroracemic acid. Another interesting synthesis of this compound is from acetonyl acetone and pyrrole.[2]



Acetonyl acetone — Pyrrole — 4 : 7-Dimethyl-indole.

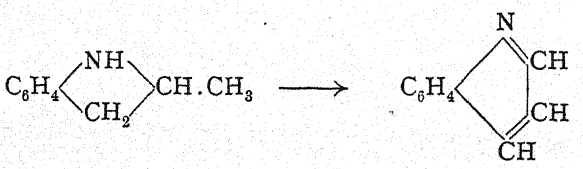
Alkyl-indoles resemble the parent compound in being of weakly basic character. The methyl derivatives have a repulsive smell, and on fusion with potash yield indole-carboxylic acids. Most of them give the pine splint reaction.

Indole and its homologues (compare pyrrole, p. 613) react with chloroform or bromoform in such a way that the ring is extended and quinoline derivatives are produced. Chloroform and α-methyl-indole, for example, give β-chloro-quinaldine:



α-Methyl-indole — β-Chloro-quinaldine.

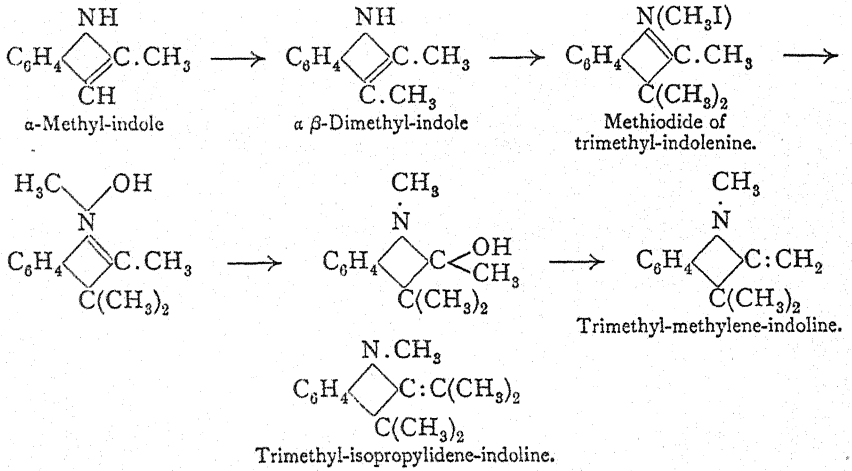
The distillation of secondary hydro-methyl-indole derivatives over zinc dust also leads to the formation of the corresponding quinoline compounds.



Hydro-α-methyl-indole, α-Methyl-indoline. — Quinoline.

[1] Bischler, *Ber.*, 1892, **25**, 2860. [2] *Ber.*, 1904, **37**, 4236.

The **behaviour of indole and alkyl-indoles on treatment with alkyl iodides** is of interest.[1] $\alpha\beta$-Dialkyl-indoles are first formed, without any alteration of the imino-group: *e.g.* α-methyl-indole yields $\alpha\beta$-dimethyl-indole. This, however, is only an intermediate phase. On further interaction with methyl iodide a rearrangement of the valency bonds takes place (transformation into the pseudo-form), the chief product being the methiodide of trimethyl-indolenine, together with a little hydriodide. On treatment with alkalis the first of these undergoes a remarkable change and is converted into trimethyl-methylene-indoline, which with methyl iodide takes up two more methyl groups to form trimethyl-isopropylidene-indoline. Even this, however, does not represent the end of the reaction, since the last-named compound may on the one hand yield a methiodide, and on the other its hydriodide under the influence of heat may exchange the isopropyl group for one of the methyl groups in the β-position. With the methylene group thus regenerated the above process may then repeat itself. The course of these reactions is indicated in the following scheme:



Skatole, *β-methyl-indole*, $C_8H_5(CH_3)NH$, is the best known homologue of indole. It is produced together with a little indole from albuminous matter by putrefaction or fusion with potash, and is also present in human fæces. As described on p. 630, it can be prepared from propylidene-phenylhydrazone. It crystallises in plates, m.p. 95°, b.p. 268°, and has a powerful and repugnant smell.

α-Methyl-indole can be obtained from acetone-phenylhydrazone. It melts at 60°, boils at 268° and resembles indole in smell. *N-Methyl-indole* is an oil of boiling-point 240°, formed by eliminating carbon dioxide from the acid obtained from methyl-phenyl-hydrazine and pyroracemic acid. It has not the unpleasant smell of skatole.

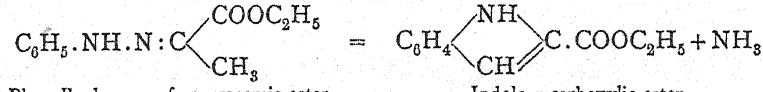
[1] Ciamician, *Ber.*, 1904, **37**, 4227.

INDOLE CARBOXYLIC ACIDS

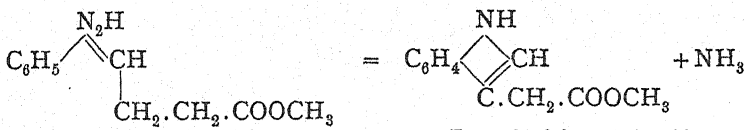
Most of the acids known in this series have been prepared by Fischer's method (previously described), which consists in heating the hydrazones of ketonic or aldehydic acids, such as pyroracemic acid and laevulinic acid, with zinc chloride.

They may also be prepared in the manner already indicated by fusing alkyl-indoles with potassium hydroxide, or by the combined action of sodium and carbon dioxide on indoles.

The acids are solid, odourless compounds with distinctly acidic and very little basic character. They easily decompose into carbon dioxide and derivatives of indole.



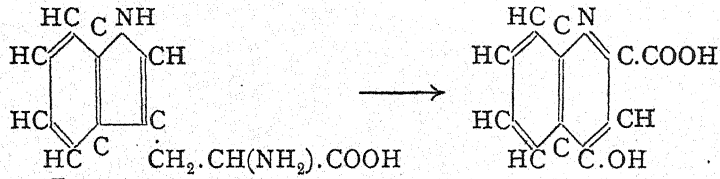
Phenylhydrazone of pyroracemic ester — Indole-α-carboxylic ester.



Phenylhydrazone of β-aldehydo-propionic ester — Ester of indole-3-acetic acid.

Indole-3-acetic acid (formula see above) is formed during the decomposition of proteins, and has been synthesised by Ellinger according to the methods just quoted.[1] It crystallises in small plates which melt at 164°, and on heating above its melting-point decomposes into skatole and carbon dioxide. For a long time this acid was assumed by a number of chemists to be 3-methyl-indole-2-carboxylic acid, and it will therefore be found frequently described as *skatole carboxylic acid.*

Tryptophane is the compound which gives rise to all the derivatives of indole formed during the putrefaction of proteins. It was first discovered by Hopkins and Cole [2] among the products of pancreatic digestion of casein. In the organism of the dog it is converted into kynurenic acid. Tryptophane has the following structure [3]:

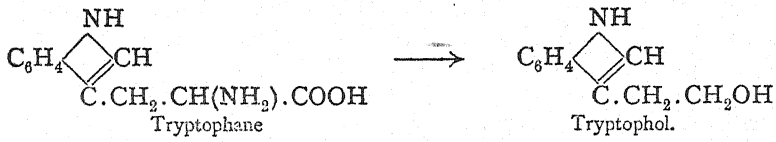


Tryptophane — Kynurenic acid, 4-hydroxy-quinoline-2-carboxylic acid.

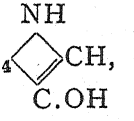
Tryptophol, 3-*indolyl-ethyl alcohol*, is formed in a similar manner to tyrosol (see p. 458) when yeast is allowed to grow in a solution of tryptophane containing the usual addition of sugar and inorganic salts,

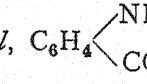
[1] A. Ellinger, *Ber.*, 1904, **37**, 1801; 1905, **38**, 2884; 1906, **39**, 2515. [2] Hopkins and Cole, *Journ. of Physiol.*, 1901, **27**, 418. [3] Ellinger and Flamand, *Ber.*, 1907, **40**, 3029. R. Majima, *Ber.*, 1922, **55**, 3859; 1924, **57**, 1453.

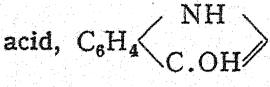
or when tryptophane is fermented directly with much sugar and compressed yeast.[1] It crystallises in needles or plates, and melts at 59°.

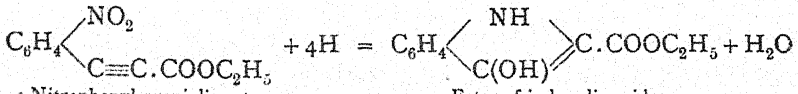


HYDROXY DERIVATIVES OF INDOLE

Indoxyl, 3-hydroxy-indole,  , is present in the form of the potassium salt of indoxyl-sulphuric acid in the urine of mammals. It can be prepared by decomposing indoxylic acid with warm water. Synthetic methods of formation will be described in connection with indigo. It forms bright yellow crystals, m.p. 85°; it cannot be satisfactorily distilled *in vacuo*, but may be partially volatilised without decomposition by heating in air or with slightly superheated steam. The vapours have a fæcal odour. When heated with potassium bisulphate indoxyl yields the salt of indoxyl-sulphuric acid, $C_8H_6N.O.SO_3K$, which on warming with acids easily reverts to indoxyl. In acid solution indoxyl has a strong tendency to resinify, and in alkaline solution it is readily oxidised, even by atmospheric air, to give indigo. It is an intermediate in the preparation of indigo by the phenyl glycine process (see p. 639).

According to the above formula, which is generally assumed for the solid compound, indoxyl contains the grouping —C(OH)=CH—. The presence of the hydroxyl group can be confirmed experimentally, but in many ways the compound reacts as the keto-form with the group —CO—CH_2—, thus giving rise to derivatives of the hypothetical *pseudo-indoxyl*,  .

Indoxylic acid,  , is of importance since it occurs as an intermediate product in the technical synthesis of indigo from phenylglycine-*o*-carboxylic acid. Its ethyl ester is obtained by reducing *o*-nitrophenyl-propiolic ester with ammonium sulphide.

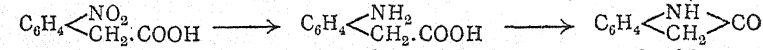


o-Nitrophenyl-propiolic ester — Ester of indoxylic acid.

As mentioned above, it readily breaks up into carbon dioxide and indoxyl; with oxidising agents it yields indigo blue, and on heating with sulphuric acid is converted into the sulphonic acid of indigo blue.

[2] F. Ehrlich, *Ber.*, 1912, **45**, 883.

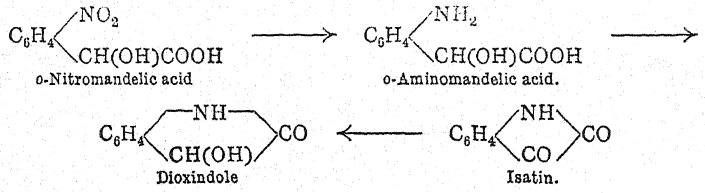
Oxindole is the lactam or inner anhydride of *o*-amino-phenylacetic acid. It is produced by reducing either *o*-nitro-phenylacetic acid or dioxindole with tin and hydrochloric acid, or by reducing isatin with sodium amalgam.



o-Nitrophenylacetic acid — *o*-Aminophenylacetic acid — Oxindole.

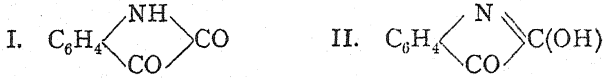
Oxindole crystallises in colourless needles, m.p. 120°, and possesses basic as well as acidic character, being soluble in both acids and alkalis. The action of alkalis at higher temperatures ruptures the indole ring to form salts of *o*-amino-phenylacetic acid. Oxidising agents convert it first into dioxindole.

Dioxindole is the lactam of *o*-amino-mandelic acid, and is formed in an analogous manner to oxindole by reduction of *o*-nitromandelic acid with zinc dust and acetic acid, and also by reduction of isatin. It crystallises in colourless prisms, m.p. 180°. On oxidation it yields isatin, and on reduction oxindole.



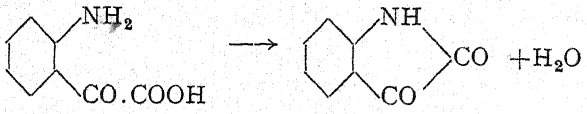
o-Nitromandelic acid — *o*-Aminomandelic acid. — Dioxindole — Isatin.

Isatin may react according to either of the formulæ I or II, and is therefore tautomeric.

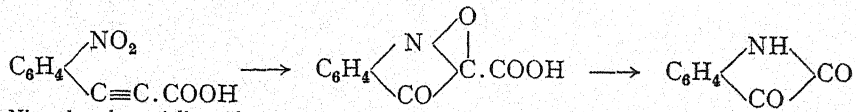


Structure I is generally ascribed to isatin in the solid state and in acid solution.[1] In salts [2] or alkaline solution, on the other hand, it possesses the structure II. Isatin is therefore an inner anhydride which may react either as the *lactam* (I) or *lactim* (II) of *o*-amino-benzoylformic acid, $NH_2.C_6H_4.CO.COOH$ (isatic acid).

It is formed by oxidation of indigotin with nitric or chromic acid, and also by oxidation of oxindole and dioxindole. Among synthetic methods of preparation may be mentioned (*a*) the elimination of water from *o*-amino-benzoyl formic acid



and (*b*) the treatment of *o*-nitro-phenyl-propiolic acid with aqueous potassium hydroxide.



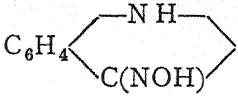
o-Nitrophenyl-propiolic acid — Isatogenic acid — Isatin.

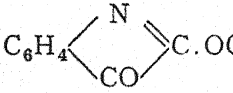
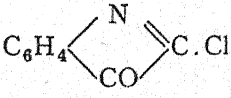
Isatin crystallises in orange-red prisms, which melt at 200° ; it dissolves

[1] From a comparison of the absorption spectra of isatin and its N-methyl and O-methyl ethers, Hartley and Dobbie concluded that isatin possessed the lactam structure. Later work by R. A. Morton and E. Rogers (*J. C. S.*, 1925, 2698) and by R. G. Ault, E. L. Hirst and R. A. Morton (*J. C. S.*, 1935, 1653) indicates that the spectra of the two methyl ethers show slight differences only and afford little information as to the structure of isatin. [2] Hantzsch, *Ber.*, 1921, 54, 1257.

sparingly in water, and readily in alcohol and ether. When heated, it volatilises with partial decomposition. It dissolves in alkalis, and if dilute solutions are employed the change from lactam to lactim structure (I to II) can be followed, the purple red colour of the N-salt passing at the ordinary temperature into the bright yellow of the O-salt. If the solution is warmed, the ring opens with the production of the alkali salt of *o*-amino-benzoyl-formic acid or *isatic acid*, $NH_2.C_6H_4.CO.COOH$.

When fused with caustic alkali isatin yields aniline, and with dilute nitric acid it is oxidised to nitro-salicylic acid. From these reactions it was concluded that the compound contains a nitrogen and a carbon atom in direct union with the benzene nucleus. Baeyer's investigation of the reduction products of isatin—dioxindole, oxindole and indole—finally led to the constitution of the compound being established, and therewith that of indigo. The above formula for isatin, which had been proposed as early as 1869 by Kekulé, was also supported by the work of Claisen and Shadwell, who first showed that isatic acid was identical with *o*-amino-benzoyl-formic acid, and that isatin was its inner anhydride.

The presence of a keto group in isatin is revealed by the usual reactions. The compound unites with sodium bisulphite and gives a hydrazone with phenyl-hydrazine. With hydroxylamine it yields *isatoxime*,  , which is identical with the nitroso-oxindole obtained by the interaction of oxindole with nitrous acid.

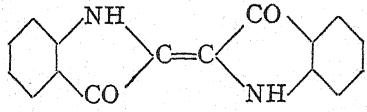
A number of isatin derivatives corresponding to the lactim structure (II) are also known. For example, when the red silver salt of isatin is treated with methyl iodide the *methyl ether of isatin*,  , is formed, which crystallises from benzene in blood-red prisms of melting-point 101° to 102°. When warmed in benzene solution with phosphorus pentachloride, isatin yields *isatin chloride*,  , a brown crystalline compound which reverts to isatin on treatment with alkalis, and with ammonium sulphide gives indigo blue. Halogens react with isatin to form substitution products, and nitric acid converts it into nitro-isatin, $C_6H_3(NO_2).C_2O_2NH$.

Isatin gives a number of colour reactions. It condenses with thiophene to give the blue dye-stuff *indophenine*, $C_{12}H_7NOS$ (see p. 626), and with pyrrole to yield the blue *pyrrole-indophenine*, $C_{24}H_{18}N_4O_3$.

Indigo Blue, Indigotin

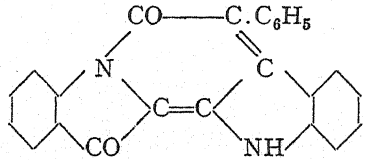
Indigo blue or indigotin is the chief constituent of commercial indigo, the earliest and one of the most important of dye-stuffs. It is mentioned by Dioscorides and Plinius, and in the thirteenth century Marco Polo

described its preparation in India. The dye was rapidly adopted in Europe, and after the discovery of the sea route to India was imported in large quantities. Even to-day much of the natural indigo is obtained



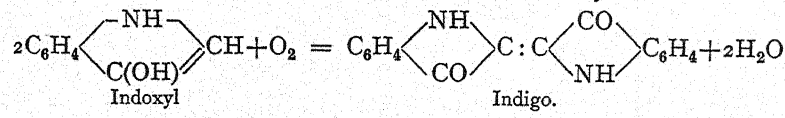
from India, although this is being displaced to an ever-increasing extent by the synthetic product. Indigo is of special importance for the dyeing of wool and is also used for cotton.

Structure of Indigo.—The molecular structure for indigo already given is deduced from the oxidation of the dyestuff to isatin by means of nitric or chromic acid, and from syntheses described later. Theoretically, indigo should exist in two geometrical isomers, of *cis* and *trans* types respectively. Only one form is known in practice, however, and X-ray analysis [1] has shown this to possess a centre of symmetry (see p. 41). Indigo must therefore have the *trans* structure. This is in agreement with the fact that *trans* forms are in general more stable than the *cis* isomers, and with the chemical properties of indigo. Phenyl acetic ester, $C_6H_5.CH_2.COOEt$, condenses with indigo, a reaction which is only satisfactorily formulated on the assumption of a *trans* structure.



Occurrence and Production of Natural Indigo.—Indigo is prepared from a variety of plants, more particularly from those of the genus *indigofera* (India, China, Central America) and from woad (Hungary, France). In these sources it is not present as such, but in the form of **indican,** which is probably the glucoside of indoxyl,[2] $C_8H_6ON(C_6H_{11}O_5)$. Indican has a bitter taste, is laevorotatory and crystallises from water in prisms containing $3H_2O$. Under the influence of certain ferments, or when treated with dilute acids, it is hydrolysed into glucose and indoxyl, and the latter in contact with atmospheric oxygen becomes oxidised to indigo.

$$\underset{\text{Indican}}{C_{14}H_{17}NO_6}+H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6}+\underset{\text{Indoxyl}}{C_8H_7NO}$$



The preparation of indigo in this manner is a comparatively simple process. Shortly before flowering the plants are cut down and brought into large stone cisterns or vats containing water at about 50°. Hydrolysis

[1] Reis and Schneider, *Z. Krist.*, 1928, **68**, 543. [2] See Macbeth and Pryde, *J. C. S.*, 1922, **121**, 1660.

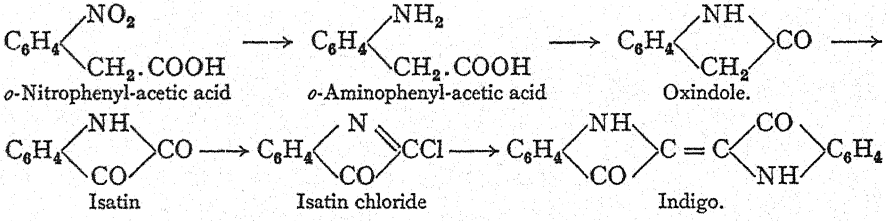
of the indican sets in, possibly assisted by the action of enzymes, and glucose and indoxyl are formed, the decomposition being complete in about ten to twelve hours. Ammonia is then added to the liquid and it is run off into vats at a lower level. Here it is "beaten," *i.e.* brought into intimate contact with air by vigorous stirring with a stirrer or wheel. In this way the indoxyl is oxidised to indigo, which separates out in the form of blue flakes. The indigo is allowed to settle, and washed several times with water. It is finally boiled out with water, filtered and dried.

The natural indigo of commerce obtained in this way consists of blue lumps with a variable content of indigotin. Java indigo, for example, contains 60 to 80 per cent. of *indigo blue*, together with *indigo red* (indirubin, see p. 643), *indigo brown*, a glutinous substance known as indigo gelatin or indigo gluten, and ash. These substances may be removed by treating the indigo successively with water, dilute acetic acid, alkalis and alcohol.

Synthesis of Indigo Blue

From the theoretical as well as the technical point of view the syntheses of indigo blue rank among the highest achievements of synthetic organic chemistry. One of these has already been mentioned in connection with indoxylic acid and isatin. In the succeeding pages a short description is given of three syntheses possessing a purely scientific interest, followed in more detail by an account of the methods actually employed on the preparative scale.

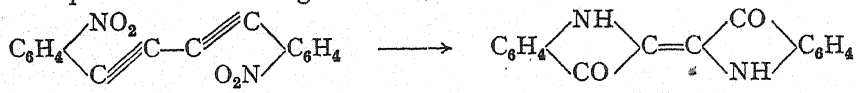
1. The first and historic synthesis of indigo was carried out by Baeyer in the following stages[1]: *o*-Nitrophenyl-acetic acid was reduced to *o*-aminophenyl-acetic acid, which was readily converted into its lactam, oxindole. The latter, on treatment with nitrous acid, gave isonitroso-oxindole, and the amino-oxindole obtained from this by reduction was transformed into isatin by the use of a mild oxidising agent. By treatment with phosphorus pentachloride isatin gave isatin chloride, which with zinc dust was reduced to indigo blue.



2. Among other early syntheses of indigo that from *o*-dinitro-diphenyl-diacetylene may be quoted, since it proves that in indigo the two indole nuclei are united to one another through a C-linking. The starting-point in this case was *o*-nitrophenyl-propiolic acid, which on boiling with water gave *o*-nitrophenyl-acetylene, $NO_2.C_6H_4.C:CH$. The copper compound of the latter, on oxidation with potassium ferricyanide, was converted

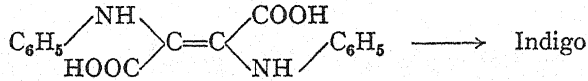
[1] Baeyer, *Ber.*, 1870, 3, 514; 1878, 11, 1228, 1296; 1879, 12, 456.

into *o*-dinitro-diphenyl-diacetylene, and this, on treatment with sulphuric acid added on two molecules of water, yielding a product from which on subsequent reduction indigo was obtained.[1]



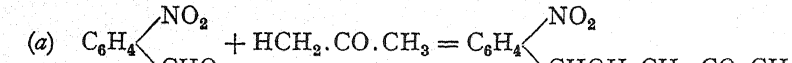
o-Dinitro-diphenyl-diacetylene Indigo.

3. A later synthesis of Salmony and Simonis,[2] involving the elimination of water from dianilido-maleic acid, also shows the presence of a link between the *a*-carbon atoms of indigo blue.

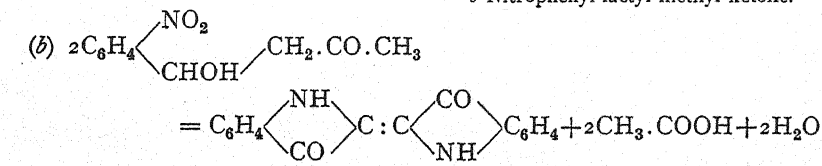


Dianilido-maleic acid.

4. The synthesis discovered by Baeyer and Drewson[3] in 1882 is distinguished by its simplicity and ease of operation. It consists in warming *o*-nitrobenzaldehyde with acetone and aqueous alkali, when *o*-nitrophenyl-lactyl methyl ketone is first produced as an intermediate product by a condensation of the aldol type :

(*a*) 

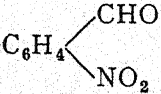
o-Nitrophenyl-lactyl methyl ketone.

(*b*) 

Indigo.

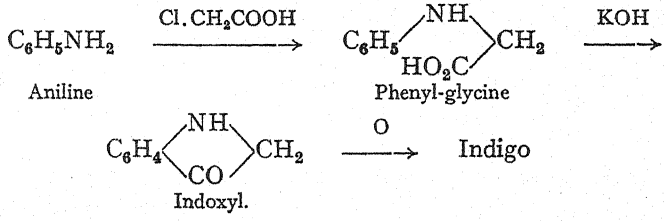
That part of the process formulated under (*a*) was used technically for a considerable time, the bisulphite compound of the above ketone being employed under the name of **indigo salt** for the generation of indigo in printing fabrics. Nevertheless, this method is not suitable for the manufacture of indigo on a large scale, owing to the difficulty of producing sufficient quantities of *o*-nitrobenzaldehyde.

By employing substituted *o*-nitrobenzaldehydes this synthesis may be used to prepare substitution products of indigo. Thus 2 : 4-dinitrobenzaldehyde,[4] on condensation with acetone in the presence of alkali, yields the corresponding **dinitro-indigo,** a dye of greenish-blue tint.

Indigo can also be obtained from other compounds of similar type, *e.g.* from the aldehyde of *o*-nitrophenyl-β-hydroxy-propionic acid,  , formed by condensing *o*-nitrobenzaldehyde with acetaldehyde.

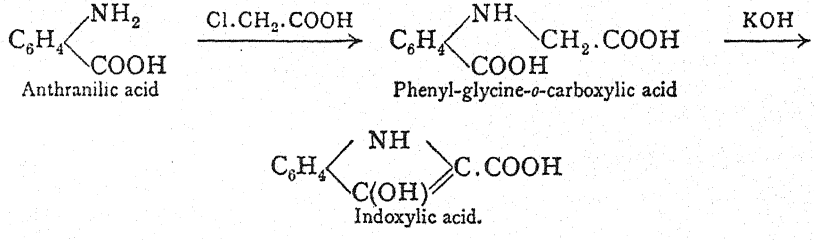
[1] Baeyer, *Ber.*, 1882, **15**, 50. [2] *Ber.*, 1905, **38**, 2580. [3] *Ber.*, 1882, **15**, 2856 ; **16**, 2205. *Ann.*, 1894, **284**, 154. [4] Sachs, Kempf and Everding, *Ber.*, 1902, **35**, 1224, 1236, 1265, 2704. Friedländer and Cohn, *Monats.*, 1902, **23**, 543, 1003.

5*a*. In 1890 a synthesis was proposed by Heumann [1] which for the first time gave promise of the successful manufacture of indigo on the technical scale, in so far as the requisite raw materials could be readily and cheaply obtained. It consisted in allowing monochloracetic acid to interact with aniline to form phenylamino-acetic acid (phenyl-glycine,



phenyl-glycocoll), converting this into indoxyl by fusion with potash, and oxidising the indoxyl to indigo with atmospheric oxygen.

5*b*. As this process only gave a small yield of indigo, Heumann modified it by using phenyl-glycine-*o*-carboxylic acid (prepared by condensing chloracetic acid with anthranilic acid) in place of phenyl-glycine in the potash fusion. The indoxylic acid so obtained was converted into indigo by treating its alkaline solution with air.



The discovery of a cheap method of preparing anthranilic acid from naphthalene, already described on pp. 448 and 452, enabled the above synthesis to be operated commercially. As now carried out, the process starts with the cheap raw material naphthalene and passes through the following stages :

Naphthalene ⟶ *phthalic acid* ⟶ *anthranilic acid* ⟶ *phenyl-glycine-o-carboxylic acid* ⟶ *indoxylic acid* ⟶ *indoxyl* ⟶ *indigo.*

As a result of this synthesis of indigo, **phenyl-glycine-*o*-carboxylic acid** (m.p. 215° with decomp.) and other aryl glycines have attracted a considerable amount of interest, and other methods have been developed for their industrial preparation.

For example, anthranilic acid reacts with formaldehyde and hydrogen cyanide to form the nitrile of phenyl-glycine-*o*-carboxylic acid, which on hydrolysis yields the free acid, $C_6H_4\langle^{COOH}_{NH.CH_2.COOH}$.

The same reaction may be applied to aniline, which on treatment

[1] *Ber.*, 1890, **23**, 3043, 3431 ; 1891, **26**, 225. *J. pr. Ch.*, 1891, **43**, 111 ; 1898, **57**, 198.

with formaldehyde and potassium cyanide gives the nitrile of phenyl-glycine, and on further hydrolysis **phenyl-glycine** itself.

$$\underset{}{C_6H_5.NH_2} + \underset{\text{Formaldehyde}}{H.CH:O} + KCN + H_2O = \underset{\text{Salt of phenyl-glycine.}}{C_6H_5NH.CH_2.COOK} + NH_3$$

According to Bucherer, the technical preparation of phenyl-glycine is best effected by converting aniline and formaldehyde into anhydro-formaldehyde-aniline, $C_6H_5N:CH_2$, combining this with sodium bisulphite, and treating the resulting sulphonic derivative, $C_6H_5.NH.CH_2.SO_3Na$, with potassium cyanide.

In general, when sulphonates of the formula $R.NH.CHR'.SO_3Na$ are treated in aqueous solution with potassium cyanide they yield nitriles of aryl-glycines, as shown in the following equation (R=aryl group).[1]

$$R.NH.CH\begin{cases}SO_3Na\\R'\end{cases} + KCN \longrightarrow R.NH.CH\begin{cases}R'\\CN\end{cases} + NaKSO_3$$

The same compounds also result from the condensation of amine hydrochlorides with aldehydes, ketones and their derivatives, in the presence of solid potassium cyanide suspended in benzene, ether or ligroin.

$$R.CHO + R'.NH_2HCl + KCN = KCl + H_2O + R.CH\begin{cases}NH.R'\\CN\end{cases}$$

Phenyl-glycine-*o*-carboxylic acid can also be obtained from *o*-chloro-benzoic acid and glycine:

$$C_6H_4\begin{cases}COOH\\Cl\end{cases} + H_2N.CH_2.COOH = C_6H_4\begin{cases}COOH\\NH.CH_2.COOH\end{cases} + HCl$$

This method is not expensive, as glycine can be prepared in good yield from chloracetic acid and ammonia.

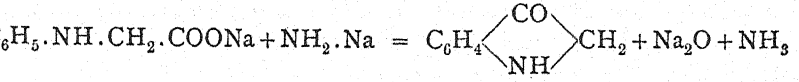
A detailed investigation of derivatives of phenyl-glycine-*o*-carboxylic acid has revealed the fact that its esters and N-acylated and N-alkylated derivatives have a much greater tendency towards the formation of the indole ring than the unsubstituted acid.[2] Thus the compound I is transformed into II merely on shaking with dilute alkali.

$$\text{I.}\quad C_6H_4\begin{cases}N\begin{cases}CH_3\\CH_2.COOCH_3\end{cases}\\COOCH_3\end{cases} \longrightarrow \text{II.}\quad C_6H_4\begin{cases}N\begin{cases}CH_3\\CH.COOCH_3\end{cases}\\CO\end{cases}$$

5*c*. A discovery of practical importance is that, in the case of phenyl-glycine derivatives, ring formation can be effected with the aid of soda-mide[3] as condensing agent. Hence phenyl-glycine as well as its *o*-carboxylic compound is now used in the preparation of indigo on an industrial scale. During the alkali fusion, as described on p. 639, phenyl-glycine undergoes partial decomposition in consequence of the high

[1] Bucherer and Grolée, *Ber.*, 1906, **39**, 986. *Cf.* also Zelinsky and Stadnikoff, *Ber.*, 1906, **39**, 1722. [2] Vorländer and co-workers, *Ber.*, 1900, **33**, 553, 556, 3182; **34**, 1646, 1649, 1854; **35**, 700. [3] Sodamide is prepared by leading ammonia through liquid sodium.

temperature required (300° to 350°), and therefore gives a very low yield of indigo. When sodamide is used, however, a much lower temperature suffices (180° to 240°), resulting in a greatly increased yield of the dye-stuff.

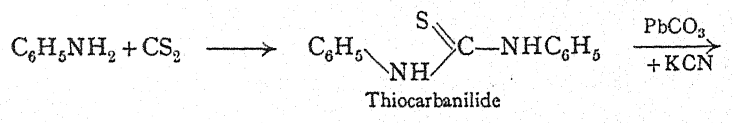


The *sodamide process*, which permits the use of phenyl-glycine, or in the first instance of aniline, as the starting material, is operated on the large scale in the following stages :

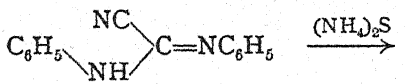
Benzene ⟶ *nitrobenzene* ⟶ *aniline* ⟶ *phenyl-glycine* ⟶ *indoxyl* ⟶ *indigo*

In recent years additional modifications, which cannot be described here, have been introduced into the Heumann synthesis.

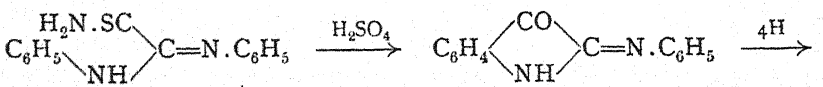
6. A method of synthesising indigo which has little in common with those described above was devised by Sandmeyer.[1] Thiocarbanilide (diphenyl-thiourea, see p. 394), obtained by the interaction of aniline and carbon bisulphide, is treated with basic carbonate of lead to remove sulphur, and then converted by means of potassium cyanide into hydrocyano-carbodiphenylimide. The latter with ammonium sulphide yields the corresponding thioamide, which on being warmed with concentrated sulphuric acid is condensed to isatin-α-anilide. By heating this with ammonium sulphide it is readily transformed into indigo.



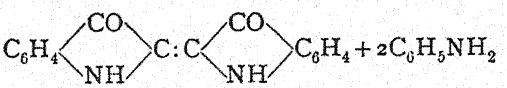
Thiocarbanilide



Hydrocyano-carbodiphenylimide.

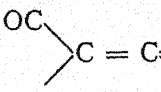


α-Isatin-anilide.



Indigo.

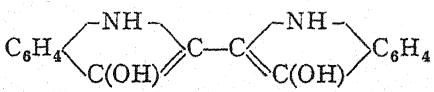
Properties of Indigo Blue

Indigo blue forms a dark blue powder possessing a reddish metallic lustre. In the light of our present knowledge of quinones and unsaturated diketones, it may be assumed that the colour of indigo is connected with the presence of the complex  in the molecule, in which

[1] *C.*, 1900, II, 927, 929, 1141.

the imido-groups play the part of auxochromes. The dye is insoluble in water, alcohol, ether, alkalis and dilute acids. It dissolves to a blue solution in hot aniline, and crystallises out from hot turpentine in blue plates. On sublimation it is obtained in coppery red prisms with a metallic glance. Cold concentrated sulphuric acid dissolves indigo without alteration, but on heating the green solution so obtained the colour changes to blue, owing to the formation of sulphonic derivatives. Chlorine and bromine in the presence of water interact with indigo mainly to yield substituted oxidation products such as chloro-isatin. In the absence of water, on the other hand, substitution products of indigo are obtained. By bromination in nitrobenzene solution, for example, according to the proportion used, there is obtained **mono-** or **dibromo-indigo,** in which the bromine atoms enter into the positions para to the imino groups. Further bromination yields **tetra-bromo indigo,** *Ciba Blue* 2 *B*, in which the two positions ortho to NH are also substituted. The brominated dyes are marked by their intensity of colour and beauty of tint, and in many cases may be used in place of indigo. These and other substitution products can also be prepared from corresponding substituted raw materials, by the methods already described for the synthesis of indigo.

With reducing agents (see below) indigo blue takes up two atoms of hydrogen and is converted into **indigo white,** which is formulated as a *di-indoxyl.*



It possesses a phenolic character and dissolves readily in alkalis, to give a solution which in the presence of air undergoes rapid oxidation with precipitation of insoluble indigo blue. This property is of great importance and is utilised in the preparation of natural indigo from the plant (see p. 636), as well as in the process of vat dyeing.

Method of Use as a Dye-stuff

Indigo is employed as a **vat dye,**[1] in the following manner. Finely-divided indigo suspended in water is first reduced. According to the material to be dyed, this may be effected by use of fermentation methods or of various chemical reducing agents, such as ferrous sulphate, stannous chloride, grape sugar, zinc dust or hydrosulphite.[2] The indigo white thus formed remains dissolved in the alkaline fluid.

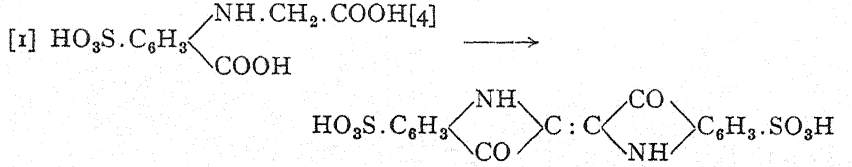
[1] For a description of the preparation and use of vat dyes see Thorpe and Ingold, *Synthetic Colouring Matters, Vat Colours* (Longmans, Green, 1923). [2] The earliest vats employed were fermentation vats, still in common use to-day for woollen goods, in which the dye-stuff is reduced by the action of micro-organisms in the presence of lime or alkalis. In the **woad vat,** for example, indigo suspended in water is treated with woad together with bran, madder, soda and lime, and the mixture is stirred and heated to 50°. Fermentation soon sets in and a yellowish solution of the calcium salt of indigo white is eventually formed. It is necessary to exclude air, as the micro-organisms are then forced to satisfy their need for oxygen by reducing the indigo blue. Compare Wendelstadt and Binz, *Ber.*, 1906, 39, 1627.

The best vat for cotton is the **hydrosulphite vat,** in which the reducing agent is the soluble sodium salt of hydrosulphurous acid, $H_2S_2O_4$. It is prepared by mixing zinc dust with a solution

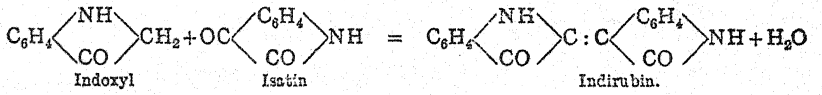
The material to be dyed is then steeped in the solution and exposed to air, when oxidation takes place and the indigo white is converted into indigo blue, which is deposited on the threads.

In **cotton printing** with indigo, the dye suspended in concentrated caustic soda is pressed into contact with the fabric, which has previously been treated with a solution of glucose. The material is then exposed to the action of steam, when indigo white is formed. This penetrates into the threads, and on subsequent exposure to air is transformed into the blue dye. The use of " indigo salt " has already been mentioned on p. 638.

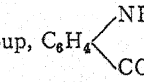
In wool dyeing use is also made of the readily soluble sodium salt of indigo-disulphonic acid (see below), which is sent on to the market in the form of a paste under the name of **indigo carmine.** This substance contains one sulphonic group in each benzene nucleus, in the para-position to the NH group, as has been shown by its synthesis by Heumann's method from anthranilido-acetic-*p*-sulphonic acid [1]:



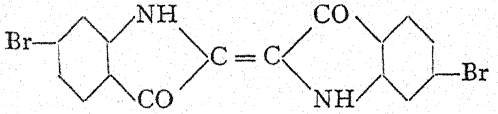
Indirubin, indigo red, occurs together with its structural isomeride indigo blue in natural indigo. It was synthesised by Baeyer by mixing weakly alkaline solutions of isatin and indoxyl, and may therefore be regarded as the indogenide of isatin:



The compound is not stable towards reducing agents and is therefore of no use as a vat dye. This drawback is not present in tetrabromo-indirubin (*Ciba Heliotrope B*), obtained by direct treatment with bromine, nor in *Thioindigo Scarlet R* (see later) in which the imino-groups are replaced by sulphur atoms.

Baeyer describes as **indogenides** those compounds in which an oxygen atom is replaced by the indogen group,  .

6 : 6′-Dibromo-indigo, of the formula



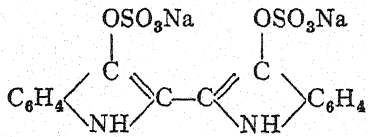
is a substance of particular interest, being identical with the *purple of the ancients* (Tyrian purple). This has been proved by a direct comparison

of sodium bisulphite and, when reduction is complete, adding milk of lime; the liquid is then drawn off from the resulting precipitate ($CaSO_3$ and zinc salts). A solution of sodium hydrate is added, together with a paste of indigo and water, and the mixture warmed with stirring to 60°, when a concentrated alkaline solution of indigo white is formed. From this " stock vat " the dyeing vats are obtained by dilution with water.

[1] Vorländer and Schubart, *Ber.*, 1901, **34**, 1860.

of the synthetic product with that prepared from the secretion of the Purple Snail, *Murex brandaris*,[1] about one and a half grammes of the dye-stuff having been isolated from 12,000 snails. The same dye can also be obtained from other molluscs,[2] such as *Murex trunculus*, *Purpura lapillus*, and *Purpura aperta*. It forms crystals of a coppery glance, and by interaction with caustic soda and sodium hydrosulphite yields a vat of weak yellow tint from which cotton is dyed a reddish-violet shade. This striking displacement of the colour of indigo results not only from the introduction of bromine, but also of chlorine and methoxyl groups in the 6 : 6′-positions. Hence substitution in the *p*-position to the CO-group exerts a quite specific influence. In the same way the effect of *p*-substitution may be traced in the derivatives of thio-indigo.

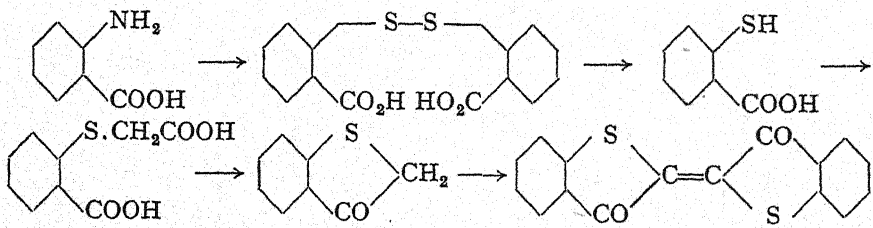
Indigosols.—In order to obviate the shrinking of woollen and silk goods when used with indigo in alkaline vats, **solubilised indigo** was introduced by Bader in 1924. Indigo is reduced to indigo white and the latter treated with pyridine-sulphur trioxide, when a sulphuric ester of leuco-indigotin is formed. The sodium salt of this compound is **Indigosol O.** It is stable in neutral solutions, from which it is directly absorbed by wool, silk or cotton. The absorbed compound is then treated on the fabric with an acid oxidising agent, when the sulphuric ester groups are hydrolysed and the regenerated indigo white converted into indigotin. Other indigosols may be prepared from derivatives of indigo in a similar manner.



Indigosol O.

Thioindigo Dyes

Dyestuffs of this group were discovered by Friedländer in 1906, as a result of experiments directed towards replacing the imino groups of indigo by sulphur atoms. The simplest compound, **thioindigo** (*thioindigo red B*, *Ciba Red*) is prepared from anthranilic acid in the following stages. By diazotisation and treatment with sodium disulphide it is converted into dithio-salicylic acid, which on reduction with iron and alkali yields thio-salicylic acid. The latter combines with chloracetic acid to form

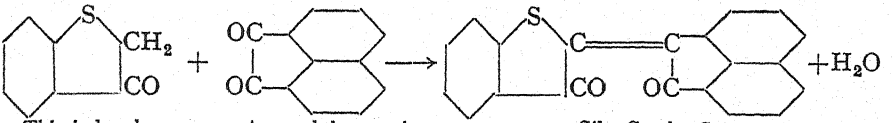


phenyl-thioglycollic-*o*-carboxylic acid, and this on fusion with alkali or sodamide gives thio-indoxyl. On oxidation with air or potassium ferri-

[1] P. Friedländer, *Ber.*, 1909, **42**, 765. *Ann.*, 1912, **388**, 23. [2] Friedländer, *Ber.*, 1922, **55**, 1655.

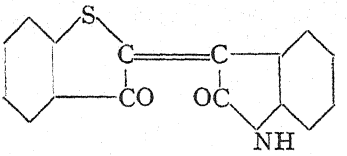
cyanide, thio-indoxyl is converted into thio-indigo, a bright bluish red dye which resembles indigo in its fastness to light and oxidation.

Other dyes of this group are made by condensing thio-indoxyl with various ketonic compounds. Thus *Ciba Scarlet G*, an excellent if somewhat expensive red dye, is obtained by use of acenaphthene quinone. It is of special value for printing.



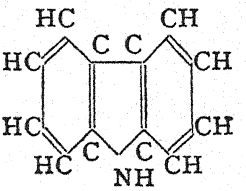
Thio-indoxyl Acenaphthene quinone Ciba Scarlet G.

Thio-indigo Scarlet R is made in a similar manner from thio-indoxyl and isatin.

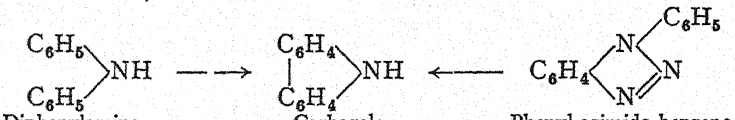


In this compound the bluish shade of thio-indigo has disappeared, to be replaced by a brilliant scarlet.

Carbazole, Dibenzo-pyrrole or Diphenylene-imine [1]



As has been mentioned on p. 549, carbazole is found in crude anthracene. The hydrogen atom of the imino-group resembles that of pyrrole in being replaceable by metals, and hence carbazole may be isolated from the above source in the form of potassium carbazole, $C_{12}H_8NK$, by distilling crude anthracene over potassium hydroxide. Another method involves treatment with suitable solvents. It is produced synthetically by various reactions, *e.g.* by leading diphenylamine through tubes heated to redness,



Diphenylamine Carbazole Phenyl-azimido-benzene.

and from thio-diphenylamine by the removal of sulphur with copper powder. It can also be obtained from *o*-amino-diphenylamine. With nitrous acid the latter yields phenyl-azimido-benzene, which on distillation parts with nitrogen to form carbazole. The last method is capable of general application, and by its means substitution products of carbazole

[1] See monograph by G. Cohn, *Die Carbazolgruppe* (Leipzig, 1919).

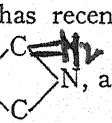
may be prepared. Carbazole is also obtained by heating *o*-diamino-diphenyl to 200° with 25 per cent. sulphuric acid, when ammonia is eliminated between the two amino-groups.

At the ordinary temperature carbazole is only sparingly soluble in the majority of solvents; it crystallises in leaflets or plates which melt at 238° and boil at 354° to 355°. Like pyrrole it is a very weak base and only forms a stable salt with picric acid. It also resembles pyrrole in giving a deep red colour with a pine splint. With isatin and sulphuric acid a blue coloration is produced.

Carbazole is an extremely stable compound. It may be distilled unchanged over zinc dust at a red heat, and is not attacked by concentrated hydrochloric acid or alcoholic potash, even at 300°.[1] Towards potassium permanganate it behaves as a fully saturated substance.

The derivatives of carbazole, which cannot be discussed here, are as yet comparatively incompletely investigated, probably owing to the difficulties encountered in working with this substance.

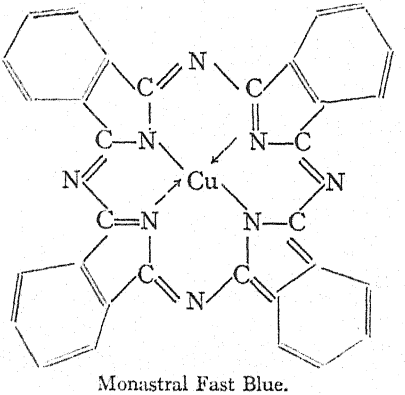
Phthalocyanines

A remarkable series of complex metallo-organic pigments known as phthalocyanines has recently been discovered, which contain the unit structure,  , and are thus derivatives of iso-indole. The first phthalocyanine, an iron compound, was isolated by chance [2] in 1928 as a dark blue crystalline substance during the preparation of phthalimide by passing ammonia into molten phthalic anhydride contained in an iron vessel. The iron was firmly attached to the molecule and was not even displaced by treatment with cold concentrated sulphuric acid. Later investigation by Linstead and his co-workers [3] led to the preparation of other derivatives and to the elucidation of their structure.

One of the best known of these compounds is **Monastral Fast Blue, B.S.**, *copper phthalocyanine*, a bright blue pigment which is employed chiefly for colouring leather, printing ink and paints. The molecular structure given below is supported by the results of X-ray analysis. It is seen to be built up of four iso-indole units linked so as to form a 16-membered arrangement of alternating carbon and nitrogen atoms. The copper atom lies in the centre and is attached to four adjacent nitrogen atoms by two co-valent and two co-ordinate valency bonds, the latter being indicated by arrows (see pp. 28, 29). The molecule is extremely stable. Copper phthalocyanine is unchanged by cold concentrated sulphuric acid and may be sublimed at 580°. With hot concentrated

[1] For hydro-derivatives of carbazole see J. Schmidt and co-workers, *Ber.*, 1907, 40, 3225; 1912, 45, 1779. Borsche, *Ann.*, 1908, 359, 49. W. H. Perkin, jun., and P. Plant, *J. C. S.*, 1924, 125, 1503. [2] By Scottish Dyes, Ltd. [3] *J. C. S.*, 1934, 1016-1035; 1936, 1719. See also J. M. Robertson, *ibid.*, 1935, 615.

nitric acid it decomposes to yield phthalimide, the same product being obtained with cold acid permanganate solution.



Monastral Fast Blue.

Monastral Blue may be prepared (*a*) by heating phthalonitrile with copper or copper salts, or (*b*) by passing ammonia into molten phthalic anhydride or phthalimide in the presence of copper compounds. By similar methods other metallic compounds are prepared. **Lead phthalocyanine** is a green pigment.

Phthalocyanine, represented by the above formula with copper removed and the two nitrogen co-valencies satisfied by two hydrogen atoms, may be prepared by dissolving the less stable magnesium phthalocyanine in cold concentrated sulphuric acid and pouring the solution on to ice. It has a greenish-blue colour with a beautiful purple reflex, and resembles the metallic derivatives in being very stable and insoluble. Reference to the formulæ given for the porphyrins on p. 814 reveals a close similarity to those of the phthalocyanines.

III

Azoles

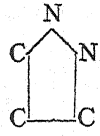
Under the name of "azoles" are included various five-membered cyclic systems containing nitrogen. In addition to carbon and nitrogen these rings may also contain oxygen or sulpur. Hence they may be derived from the compounds pyrrole, furfurane and thiophene, described in the previous chapter, by replacing methine groups with nitrogen atoms. Only the most important of these will be described in detail.

I.—PYRAZOLE GROUP

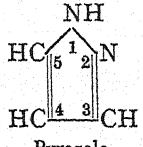
This group comprises all those compounds, the molecules of which contain a ring composed of three carbon and two nitrogen atoms arranged as follows.[1]

[1] Literature: L. Knorr, *Ann.*, 1894, **279**, 188; 1896, **293**, 1; 1903, **328**, 62. J. Schmidt, "Ueber die Pyrazolgruppe" (*Ahrens Vorträge*, vol. iv., Stuttgart, 1899).

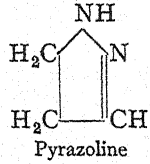
The parent substance of these compounds, pyrazole, is a pyrrole in which a methine group has been replaced by nitrogen.



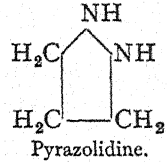
For this reason the *nomenclature of the pyrazole group* is based on that suggested by Knorr for pyrrole derivatives. Just as dihydro-pyrrole is known as pyrroline and tetrahydro-pyrrole as pyrrolidine, so the dihydro-pyrazoles are termed *pyrazolines* and the completely reduced tetrahydro-derivatives, *pyrazolidines*.



Pyrazole

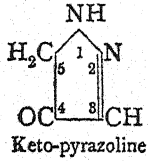


Pyrazoline

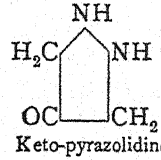


Pyrazolidine.

The position of a substituent group in the pyrazole nucleus is indicated by the numbers 1 to 5. Numbering commences with the nitrogen atom of the imino-group and proceeds in a clockwise direction to the second nitrogen atom, as in the above formula. Ketonic derivatives of pyrazoline and pyrazolidine are usually divided into two classes, viz., 4-derivatives or true ketones, such as keto-pyrazoline and keto-pyrazolidine,

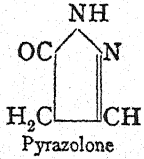


Keto-pyrazoline

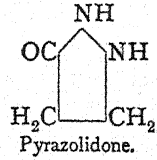


Keto-pyrazolidine

and the 3- and 5-derivatives, which are cyclic acid amides. For the latter Knorr proposed the names pyrazolone and pyrazolidone.



Pyrazolone



Pyrazolidone.

Our knowledge of the pyrazole series is largely due to the work of Knorr, who described the first representatives of this group in 1883.[1] The physical properties of these compounds and the applications which many of them, such as antipyrin, find in medicine, lend a special interest to this chapter of organic chemistry. For this reason the pyrazole group, after its discovery by Knorr, was investigated in a number of directions and—thanks to the ease with which the pyrazole ring can be formed—

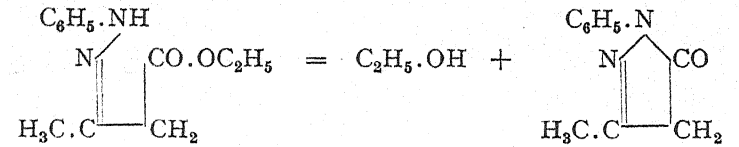
[1] L. Knorr, *Ber.*, 1884, 17, Ref. 149.

these efforts met with considerable success. Among other results, it may be mentioned that Knorr has established the existence of a peculiar type of isomerism in this series, which appears to throw some light on the structure of benzene.

General Methods of Preparing Pyrazole Derivatives

Various means of synthesising pyrazole derivatives have been developed by Knorr.

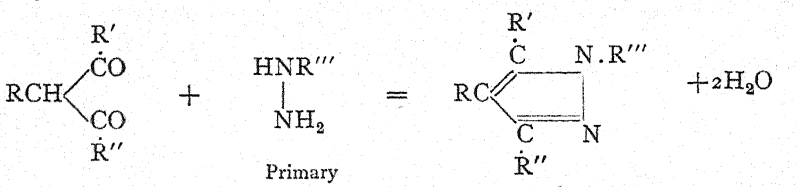
Esters of β-ketonic acids condense with hydrazines to form derivatives of pyrazolone. The reaction proceeds in two phases. A hydrazone of the ester is first produced, from which alcohol is then eliminated.



Phenyl-hydrazone of acetoacetic ester

1-Phenyl-3-methyl-5-pyrazalone.

A method similar to the above consists in the interaction of hydrazines with β-diketo-compounds of the general formula $R'.CO.CHR''.COR'''$. This has proved the most fruitful of all reactions devised for the preparation of pyrazole derivatives. On the one hand, as basic component, we may employ hydrazine hydrate itself or any primary hydrazine, and on the other, the above general formula includes all the numerous β-diketones and β-keto-aldehydes which can be prepared by the synthetic methods of Claisen and Wislicenus.

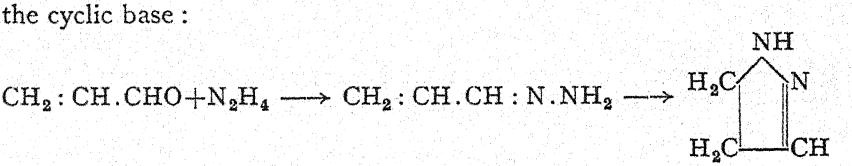


β-Diketone. Primary hydrazine. Pyrazole derivative.

Hydrazines condense with unsaturated ketones or aldehydes of the types

$$R'—CO—CR'=CHR'' \quad \text{and} \quad H—CO—CR'=CHR''$$

to give derivatives of pyrazole or pyrazoline. Thus the parent compound of the latter class, **pyrazoline,** is formed from acroleïn and hydrazine hydrate. The acryl-hydrazine first obtained isomerises spontaneously into the cyclic base :



Phenyl-hydrazones of unsaturated aldehydes and ketones, containing

a double bond in the α-position, may be transformed with great ease into the isomeric pyrazoline derivatives by boiling with glacial acetic acid.[1]

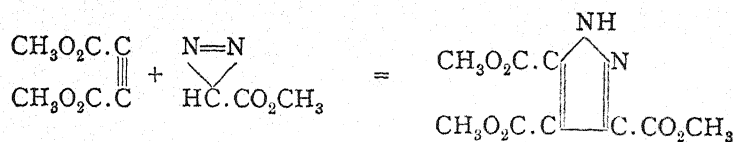
In a similar manner unsaturated acids of the acrylic acid series, R.CH : CH.COOH, react with hydrazines to give derivatives of pyrazolone or pyrazolidone.[2]

The principle of the above syntheses may be summarised in the following statement :

Compounds containing two CO-groups, or a CO- and a COOH-group, in the β-position to one another, or two doubly-linked carbon atoms adjacent to a COOH- or CO-group, react with hydrazines to give pyrazole derivatives.

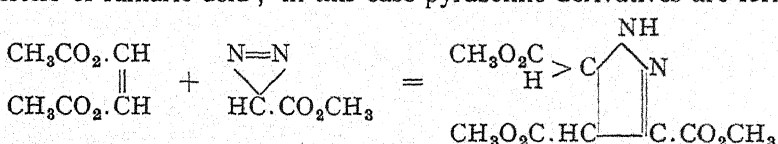
Further syntheses in this group have been effected by E. Buchner in the course of an investigation into the action of diazo-acetic ester on unsaturated compounds.[3] Pyrazole derivatives were obtained :

(*a*) By the interaction of diazo-acetic ester with esters of mono- or dibasic acids of the acetylene series,



Acetylene-dicarboxylic ester — Diazo-acetic ester — Pyrazole-tricarboxylic ester.

(*b*) By combination of diazo-acetic ester with ethylene derivatives such as esters of fumaric acid ; in this case pyrazoline derivatives are formed,



Fumaric ester — Diazo-acetic ester — Pyrazoline-tricarboxylic ester.

(*c*) By the action of diazo-acetic ester on esters of certain saturated or unsaturated halogen-substituted acids (*e.g.*, bromo-maleic acid, α-bromo-cinnamic acid, α β-dibromo-propionic acid),

$$\underset{\text{Dibromo-propionic ester}}{C_2H_3Br_3(CO_2CH_3)} + 3\underset{\text{Diazo-acetic ester}}{CHN_2(CO_2CH_3)} = \underset{\text{Pyrazole-dicarboxylic ester}}{C_3H_2N_2(CO_2CH_3)_2} + 2\underset{\text{Brom-acetic ester}}{CH_2Br(CO_2CH_3)} + 2N_2$$

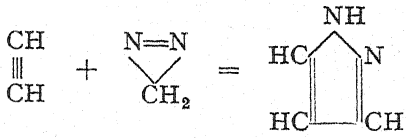
The **preparation of pyrazole** itself was first accomplished by the above methods. E. Buchner obtained it in 1889 by the prolonged action of heat on 3 : 4 : 5-pyrazole-tricarboxylic acid, the ester of which is formed, as just described, by the addition of diazo-acetic ester to acetylene-dicarboxylic ester.

Soon afterwards it was prepared by Balbiano by heating hydrazine hydrate with epichlorhydrin and chloride of zinc.

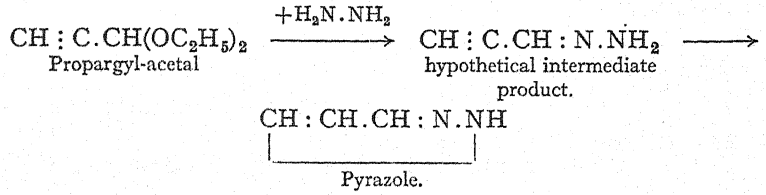
Subsequently von Pechmann discovered that acetylene and diazo-

[1] K. Auwers and co-workers, *Ber.*, 1908, 41, 4230; 1909, 42, 4411. [2] Knorr and Duden, *Ber.*, 1892, 25, 761. [3] *Ann.*, 1893, 273, 214.

methane react in a similar manner. This constitutes the simplest synthesis of pyrazole.



Pyrazole is also obtained by treating the acetal of propargyl-aldehyde [1] with hydrazine.



These simple syntheses prove that the atoms in the pyrazole ring are arranged in agreement with the formula assumed above.

Probably the best means of preparing pyrazole is from pyrazole-3 : 5-dicarboxylic acid. This is readily prepared synthetically, and on being heated decomposes smoothly into carbon dioxide and pyrazole (Knorr).

In connection with this survey of the synthetic methods available for preparing pyrazole derivatives, some reactions of the latter may be quoted which are of value in the preparation of simpler members of the series.

A reaction of special importance for the preparation of pyrazole itself consists in the elimination of carboxyl groups from pyrazole-carboxylic acids, by heating the latter above their melting-points.

The conversion of the oxygen derivatives, pyrazolones and pyrazolidones, into pyrazoles may be effected by distillation with zinc dust, or more conveniently by the action of phosphorus pentasulphide or tribromide.[2]

The oxygen of pyrazolones may also be removed by heating these substances with phosphorus oxychloride, when chloro-derivatives are formed (Michaelis).

Properties of Pyrazole and its Derivatives

The similarity in the formulæ of pyrazole and pyrrole does not extend to their properties. Pyrazole differs strongly from pyrrole in its remarkable stability and more definitely basic character.

Pyrrole turns brown in air, resinifies with extraordinary ease, and on reduction is converted into di- and tetrahydro-derivatives. Pyrazole, which crystallises in long colourless needles, m.p. 70° and b.p. 185°, is much more resistant to change.

In pyrrole the basic character is barely evident. On the other hand, pyrazole, although it gives no reaction with litmus and can be removed

[1] L. Claisen, *Ber.*, 1903, **36**, 3664. [2] R. Störmer and Martinsen, *Ann.*, 1907, **352**, 322.

from weakly acid solutions by a current of steam, nevertheless yields well-defined salts with acids.

All the chemical properties of pyrazole show it to be more nearly allied to pyridine and benzene than to pyrrole. It exhibits, to an even greater degree than thiophene, those peculiarities which were first observed in the aromatic series and are therefore associated with the term " aromatic character."

A number of facts established by Knorr clearly illustrate the **aromatic character of pyrazole :**

1. Fuming sulphuric acid converts pyrazole into a sulphonic acid, which in its reactions shows certain resemblances to the aromatic sulphonic acids.

2. In halogen derivatives of pyrazole a halogen atom attached to the nucleus is even more firmly held than in benzene derivatives.

3. When pyrazole is treated with concentrated nitric acid, hydrogen is readily exchanged for a nitro-group. Like the aromatic nitro-compounds, 4-nitro-pyrazole and its derivatives can be reduced to amino-compounds.[1]

4. Amino-pyrazole resembles the aromatic bases in its behaviour. It gives a colour reaction with a solution of bleaching powder, and is readily diazotised.

5. Diazo-pyrazoles can be coupled with phenols to form azo-dyes in exactly the same manner as the aromatic diazo-compounds. They differ from most of the latter in the stability of their salts in aqueous solution. On boiling these solutions there is no visible evolution of nitrogen ; this only occurs on prolonged heating at a higher temperature. Diazo-pyrazoles, however, do not undergo the usual " diazo-reactions."

6. Pyrazolone, or 5-hydroxy-pyrazole, has a pronounced phenolic character.

7. Towards oxidising and reducing agents pyrazole shows the same remarkable stability as benzene.

8. Homologues of pyrazole resemble those of benzene in being readily oxidised to the corresponding carboxylic acids.

Hence it will be seen that the analogy between pyrazole and benzene is a far-reaching one.

The *similarity between pyrazole and pyridine* may also be illustrated by several examples. It is clearly shown in the behaviour of the double salts formed by pyrazole with platinic chloride, and in similar double salts given by pyridine and pyrazole with other metallic compounds, such as mercuric chloride, potassium platinous chloride and the sulphates of copper, zinc and cadmium.

In smell and other properties the alkyl derivatives of pyrazole so closely resemble pyridine bases that on casual examination they may easily be mistaken for them. The carboxylic acids of pyrazole also possess many points in common with those of pyridine. For example, when polycarboxylic acids of pyridine are heated, they part with carbon dioxide

[1] Knorr, *Ber.*, 1895, **28**, 715. Knorr and Stolz, *Ann.*, 1896, **293**, 58.

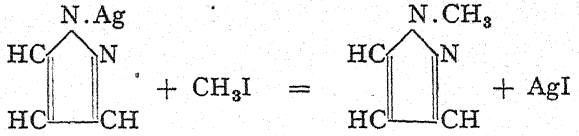
to give the mono-acid, and it is found that the carboxyl group in the α-position to nitrogen is the first to be removed. By a repetition of this process the monocarboxylic acid is converted into pyridine. The properties of 3- (or 5-) pyrazole-carboxylic acid are very closely allied to those of pyridine α-carboxylic acid (see Picolinic Acid).

Owing to the basic character of pyrazole, its resemblance to pyridine is more evident than its resemblance to benzene. Pyrazole is a weak secondary base ; as such it may be acetylated, benzoylated, and converted into derivatives of urea and urethane.[1]

It unites with alkyl iodides to form crystalline ammonium compounds. These are of importance in the preparation of homologues of pyrazole, as under the influence of heat the alkyl radical is transferred from nitrogen to a carbon atom of the nucleus. The Hofmann synthesis of aniline homologues (p. 390) can therefore be applied to the pyrazole series. As will be seen later, this reaction is also of value in the pyridine group.

A *separation of the secondary and tertiary pyrazole-bases* resulting from the above process may be effected by taking advantage of the fact that secondary pyrazoles can be quantitatively thrown out of an aqueous solution in the form of their silver salts, tertiary pyrazoles remaining unchanged.

The silver compounds are readily formed by all pyrazoles containing a free imino-hydrogen atom, and are useful for the preparation of N-alkyl substituted derivatives by double decomposition with alkyl iodides. Thus silver pyrazole and methyl iodide yield 1-methyl-pyrazole.



According to Knorr, these *N-alkyl-pyrazoles* are better prepared by distilling the corresponding pyrazole alkiodides.

An interesting regularity has been observed in connection with the physical constants of pyrazole homologues.[2] Symmetrically constituted compounds possess higher melting-points than the isomeric unsymmetrical compounds, and of the latter the tertiary derivatives melt much lower than the isomeric secondary bases.

For example :	Melting-point.	Boiling-point.
3 : 5-Dimethyl-pyrazole (symm.) . . .	107°	220°
3 : 4-Dimethyl-pyrazole (unsymm., second.) .	57° to 59°	222°
1 : 3-Dimethyl-pyrazole (unsymm., tert.) .	liquid	140° to 141°

A further difference between C-alkyl and N-alkyl derivatives is that the former usually have only a slight odour, while the latter generally have a strong smell recalling that of pyridine.

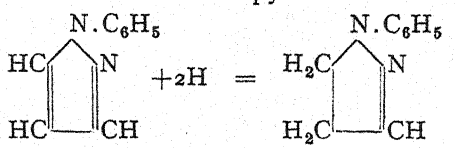
It has already been mentioned that the pyrazole nucleus is stable towards oxidising agents. The alkyl groups attached to the ring in homologues of pyrazole may be successively oxidised to carboxyl groups by use of potassium permanganate.

[1] Knorr, *Ber.*, 1895, **28**, 716. [2] For further details see Knorr, *Ber.*, 1895, **28**, 694.

In 1-phenyl-pyrazoles the benzene nucleus is more readily oxidised away than the pyrazole nucleus, as is shown by the formation of pyrazole when 1-phenyl-pyrazole is oxidised with permanganate in sulphuric acid solution (Knorr). As in the aromatic series, the benzene ring is still more easily disrupted if its stability is first lowered by the introduction of an amino or hydroxyl group. For example, the benzene ring of 1-amino-phenyl-3-methyl-pyrazole is much more readily attacked than that of 1-phenyl-3-methyl-pyrazole. A remarkable point is the stability of pyrazole derivatives under these conditions as compared with corresponding derivatives of pyrrole, the latter being completely oxidised by potassium permanganate.

The action of nascent hydrogen (from sodium and alcohol) varies with different compounds of the pyrazole group. Pyrazole itself and its homologues are apparently not attacked by sodium and alcohol.

1-Phenyl-pyrazole and its homologues, *i.e.*, those derivatives formed by the interaction of phenyl-hydrazine and β-diketo-compounds, have been shown by Knorr to be reduced to pyrazoline derivatives :



1-Phenyl-pyrazole 1-Phenyl-pyrazoline.

Pyrazoline bases obtained from phenyl-hydrazine are changed by oxidising agents, such as chromic acid, nitrous acid, ferric chloride, and hydrogen peroxide, into characteristic dyes varying from red to blue in colour. This reaction, described by Knorr as the **pyrazoline reaction,** may be used for the detection of pyrazole and pyrazoline bases derived from phenyl-hydrazine.

The reaction is conveniently carried out as follows : A small amount of the pyrazole base is dissolved in alcohol in a test-tube, and a small piece of sodium added to the boiling solution. After the metal has dissolved, the mixture is diluted with water, the alcohol distilled off, and the pyrazoline base extracted from the residue by means of ether. After removing the ether, the base is dissolved in comparatively strong sulphuric acid and a drop of a solution of sodium nitrite or potassium dichromate added, when a fine coloration (red to blue) is produced.

Pyrazoline and its Derivatives.—Pyrazoline derivatives differ considerably in their properties from those of pyrazole, owing to their much lower stability. This is another indication of the aromatic nature of pyrazole, since it is almost a characteristic of aromatic compounds that the addition of two hydrogen atoms to the ring results in diminished stability.

The pyrazolines give the reactions of aliphatic derivatives, resembling unsaturated compounds in their behaviour towards permanganate and nascent hydrogen. They resemble hydrazones in the manner in which they are hydrolysed by mineral acids, and aldazines in their decomposition into gaseous nitrogen and nitrogen-free substances. The presence of a

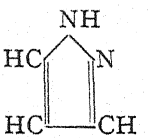
five-membered ring is only revealed in the ease with which pyrazolines are converted into pyrazoles.

Pyrazoline and its homologues are weak bases. In general they only dissolve in concentrated acids, forming unstable salts which dissociate on the addition of water. The parent substance, **pyrazoline,** an oil of boiling-point 144°, is the most stable of all these compounds.

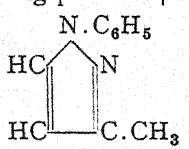
The *pyrazolidines*, or completely reduced pyrazoles, have not been thoroughly investigated owing to their instability. They possess strong reducing properties and readily give up hydrogen to form pyrazolines.

Derivatives of Pyrazole—Tautomerism in the Pyrazole Series

As the result of an investigation into the synthetic derivatives of 1-phenyl-pyrazole,[1] Knorr assigned to the then unknown pyrazole the following constitution :—

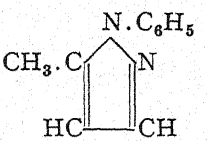


The problem of the structure of pyrazole entered a new phase in 1893, when Knorr and Macdonald showed that the oxidation of the well-known isomeric compounds 1-phenyl-3-methyl-pyrazole and 1-phenyl-5-methyl-pyrazole, or their amino-derivatives, gave one and the same methyl pyrazole [2] of boiling-point 204°.



1-Phenyl-3-methyl-pyrazole

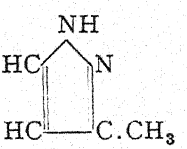
Crystalline, m.p. 37°.
B.p. 254° to 255°.
Methiodide, m.p. 144°.



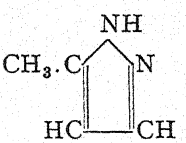
1-Phenyl-5-methyl-pyrazole.

Colourless oil, b.p. 254° to 255°
Does not solidify at —20°.
Methiodide, m.p. 296°.

By this method it is therefore not possible to obtain the two methyl-pyrazoles of the formulæ



and



corresponding to the above phenyl-methyl-pyrazoles.

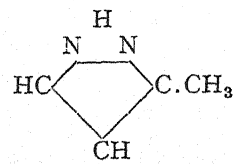
Knorr and Macdonald also failed to observe the production of isomeric methyl-pyrazoles on condensing hydrazine hydrate with oxy-methylene-acetone. On the other hand, Claisen and Roosen found that

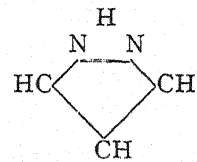
[1] *Ber.*, 1890, **23**, 1103. [2] Knorr and Macdonald, *Ann.*, 1894, **279**, 188. For isomerism in the pyrazole series see also K. von Auwers, *Ber.*, 1922, **55**, 3880; 1925, **58**, 528; 1927, **60**, 1730.

phenyl-hydrazine reacted with oxymethylene-acetone to form two isomeric phenyl-methyl-pyrazoles.[1]

Methyl-pyrazole, b.p. 204°, may therefore be a mixture of the two desmotropic forms, 3-methyl-pyrazole and 5-methyl-pyrazole, in a state of continuous and rapid interconversion.

For these reasons Knorr described the compound as **3-(5)-methyl-pyrazole** and formulated it as I below :

I. 

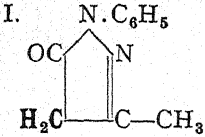
II. 

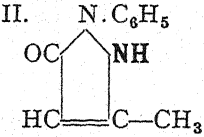
The accuracy of this conclusion was confirmed by the discovery that methyl-pyrazole could react simultaneously in the sense of a 3- and a 5-methyl-pyrazole.

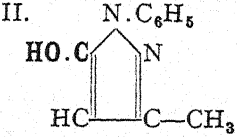
It is therefore assumed that the 1-hydrogen atom in pyrazole is not permanently attached to a given nitrogen atom, but is linked sometimes to one and sometimes to the other, with necessary readjustment of the double bonds, as indicated in formula II. But the actual position of equilibrium varies with the nature of the substituent group or groups attached to the pyrazole ring and may in extreme cases correspond to a definite fixed structure.[2]

In addition to the above tautomerism of 3-(5)-methyl-pyrazole, a second and very peculiar type of tautomerism has been observed in the pyrazole series in connection with **1-phenyl-3-methyl-5-pyrazolone,** the parent compound of antipyrine, which is usually formulated as I. It is prepared in large quantities as an intermediate product in the manufacture of antipyrine, by condensing acetoacetic ester with phenyl-hydrazine (see p. 265).

According to Knorr,[3] this extremely reactive compound may react simultaneously in the three tautomeric forms :

I. 
Methylene form

II. 
Imine form

III. 
Phenolic form.

In this case we are therefore dealing with a very complicated case of tautomerism, described by Knorr as " double tautomerism."

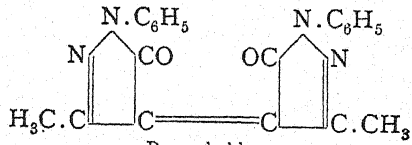
1-Phenyl-3-methyl-5-pyrazolone itself is known only in one form. Whether prepared by synthesis or from a derivative corresponding to one or other of the above three types, it is always obtained in the form of a substance of melting-point 127°, crystallising in white prisms. Which of the above three formulæ represents this compound has not yet been

[1] *Ber.*, 1891, **24**, 1888. *Ann.*, 1894, **278**, 361. [2] von Auwers, *Ann.*, 1934, **508**, 51.
[3] Knorr, *Ber.*, 1895, **28**, 706.

established with certainty, but numerous derivatives are known corresponding to each type.

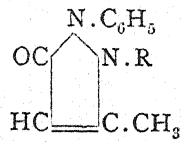
The majority of the derivatives of phenyl-methyl-pyrazolone possess the *methylene structure*.

Examples of this type are *1-phenyl-3-methyl-4-dimethyl-pyrazolone* and *pyrazole blue*. The latter is readily obtained by gentle oxidation of phenyl-methyl-pyrazolone, and represents the indigo of the pyrazole series.



Pyrazole blue.

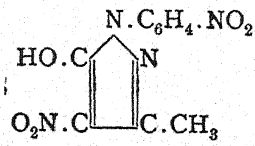
The *imine structure* is only found in the particular group of phenyl-methyl-pyrazolone derivatives known as *antipyrines* :



Proof of the imine structure of antipyrines is found in the disruption of antipyrine by means of sodium and carbon dioxide, to give the anilide of β-methylamino-crotonic acid.[1]

Three other groups of compounds must be considered as belonging to the *phenolic type*, viz., the *phenol-ethers*, *esters* and *salts* of *phenyl-methyl-pyrazolone*.

In conclusion, it may be mentioned that certain nitro-derivatives of phenyl-methyl-pyrazolone, such as *4-nitro-1-p-nitrophenyl-3-methyl-pyrazolone*, known as **picrolonic acid**,



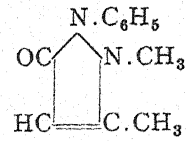
are also regarded by Knorr as nitrophenols, owing to their similarity to picric acid. Picrolonic acid yields very sparingly soluble salts, which in their properties show a close resemblance to the picrates. They are usually even less soluble than the latter, and may be employed with advantage for the isolation and identification of bases.

The arguments which lend support to each of the three competing formulæ of phenyl-methyl-pyrazolone lead to the conclusion that the acidic hydrogen atom and the double bonds occupy no fixed positions in this compound. It is the peculiar mobility of this hydrogen atom which enables tautomeric changes to be completed with such ease.

Analogous rearrangements of bonds, but without any movement of hydrogen, are also shown by antipyrine in certain addition reactions.

[1] Knorr and Taufkirch, *Ber.*, 1892, **25**, 768.

Antipyrine, *1-phenyl-2 : 3-dimethyl-5-pyrazolone*,

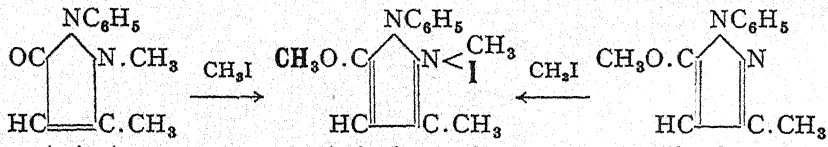


is the most important member of the pyrazole group, and is used extensively in medicine as a febrifuge. It is prepared industrially by heating 1-phenyl-3-methyl-5-pyrazolone with methyl iodide and methyl alcohol at 100° under pressure; the hydriodide of antipyrine is thus produced, from which sodium hydroxide liberates antipyrine itself. A method of preparing antipyrine which throws light upon its constitution consists in the condensation of acetoacetic ester with symmetrical phenyl-methyl-hydrazine.

It crystallises in white plates, m.p. 113°, and dissolves readily in water and alcohol. The aqueous solution is coloured red by ferric chloride, and green by nitrous acid. Antipyrine is a strong monacid base and readily forms salts, most of which are easily soluble in water.

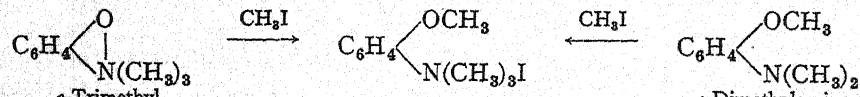
At ordinary temperatures alkyl iodides unite with antipyrine in the same manner as with the inner salts of phenol-ammonium bases, *i.e. phenol betaines*, in that iodine attaches itself to the 2-nitrogen atom of antipyrine, while the alkyl group unites with the oxygen atom. This behaviour originally led to the suggestion that antipyrines should be formulated as phenol-betaines.

From antipyrine and methyl iodide, for example, there is formed an antipyrine "*pseudo*"-methiodide,[1] which is identical with the methiodide of 1-phenyl-3-methyl-5-methoxy-pyrazole :



Antipyrine — Antipyrine *pseudo*-methiodide — 1-Phenyl-3-methyl-5-methoxy-pyrazole.

Phenol betaines unite with methyl iodide in a similar way, in the presence of caustic potash. The resulting quaternary iodides are identical with those obtained from the dimethylamino-anisoles.

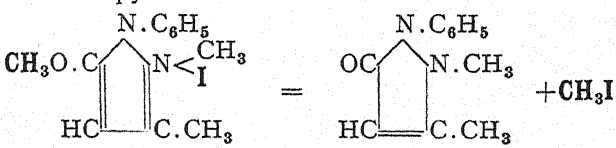


o-Trimethyl-ammonium phenoxide — *o*-Dimethylamino-anisole.

[1] Knorr terms these compounds antipyrine *pseudo*-methiodides in order to indicate their derivation from antipyrine, the term antipyrine-methiodide being reserved for the as yet unknown true methiodide. It was the formation of these *pseudo*-compounds which first led Knorr to consider whether antipyrine might not be more correctly formulated as a phenol betaine, *i.e.*, the inner salt of a phenol ammonium base. Compare also Michaelis, *Ann.*, 1902, **320**, 45; 1904, **331**, 197.

A detailed comparison of antipyrine with *o*-trimethyl-ammonium phenoxide, however, revealed the fact that, apart from the addition of alkyl iodide, these compounds were quite different in behaviour; the *pseudo*-alkiodides of both compounds had also different properties, and hence the " phenol betaine " formula for antipyrine was rejected.

On being fused, the pseudo-alkiodides of antipyrine do not break up, as might be expected, into alkyl iodide and a phenolic ether, but into alkyl iodide and antipyrine.

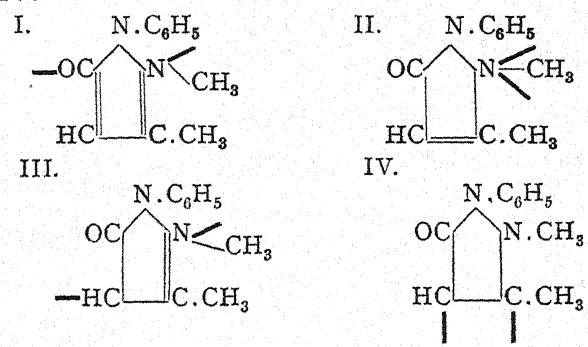


Antipyrine is also regenerated from the pseudo-methiodide by the action of alkalis, slowly in the cold and more rapidly on heating.[1]

In the above reactions it will be seen that antipyrine behaves as an unsaturated compound of type I.

Under the influence of alkalis at higher temperature, however, antipyrine and similarly constituted compounds react as unsaturated substances [2] according to formulæ II and III.

Finally, on interaction with bromine, antipyrine behaves in the sense of formula IV.



This remarkable variation in addition-reactions is explained by Knorr as being due to intramolecular movements of the hydrogen atom in antipyrine, accompanied by changes of linking.[3]

It is suggested that the 2-nitrogen atom alternates between the tri- and pentavalent states, thus permitting displacements of valency bonds similar to those assumed in the case of tautomeric compounds.

Among the great number of antipyrine molecules present in solution or the fused state there will always be some in which the valency conditions correspond to the above four types.

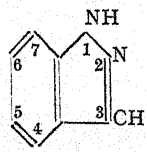
[1] An equally remarkable behaviour towards alkyl iodides, resembling the above case of antipyrine, is shown by the γ-quinolones and by nitroso-dimethylaniline (Knorr, *Ber.*, 1897, **30**, 922, 933). All these reactions involve addition to the ends of a long chain containing neighbouring double bonds, which leads to a simultaneous rearrangement of the bonds. They thus recall the cases of 1 : 4-addition studied by Thiele (p. 22). [2] Knorr, *Ann.*, 1896, **293**, 7. [3] *Ann.*, 1896, **293**, 39.

In the addition of alkyl halides in the cold, and in the production of antipyrine salts, form. I will react in preference, since the negative radical will naturally attach itself to the basic and the positive radical to the acidic point of the antipyrine molecule. Only at higher temperatures, at which the alkiodides of the phenol-ether type are no longer capable of existence, does antipyrine react with methyl iodide according to formulæ II and III. Bromine, on the other hand, unites in positions 3 and 4 (form. IV), in accordance with its tendency to add on to a double carbon linkage.

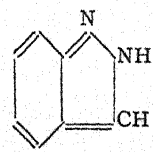
Certain other derivatives of this type are of importance, *e.g.* **salipyrine,** or antipyrine salicylate, **tolypyrine** or *p*-tolyl-dimethyl-pyrazolone, and **pyramidone** or 4-dimethylamino-antipyrine. These and other derivatives are employed medicinally, particularly as substitutes for antipyrine.

Indazoles or Benzo-pyrazoles

The ring system of the indazoles consists of a condensed benzene-pyrazole nucleus, and these compounds thus stand in the same relationship to the pyrazoles as the indoles to the pyrroles. Although the imino-hydrogen atom in indazole is not definitely located on either nitrogen atom, the parent compound gives rise to two series of N-derivatives, *e.g.* the 1- and 2-N-methyl indazoles. The position of substituents is indicated by numbers, as in the following formula:



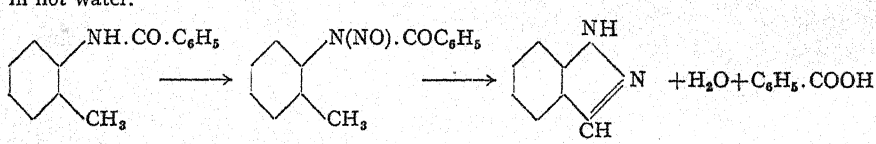
Indazole (A)



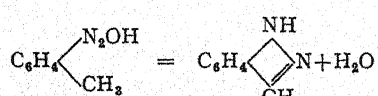
Indazole (B).

The structure of indazole has been intensively studied by Auwers and co-workers [1] and is still a matter of controversy. In all probability it is a resonance hybrid of forms A and B with A predominating.[2]

Indazole, discovered by Fischer and Tafel, is a crystalline compound, m.p. 146°, b.p. 270°. It may be prepared from benz-*o*-toluidide by dissolving it in acetic acid and acetic anhydride and passing in nitrous fumes; the resulting nitroso-compound, when heated in dry benzene, loses water and benzoic acid to form indazole, which is extracted with hydrochloric acid and then precipitated by addition of alkali. Indazole is soluble in hot water.



It is also obtained by removing the elements of water from *o*-toluene-diazo-hydroxide in neutral solution.



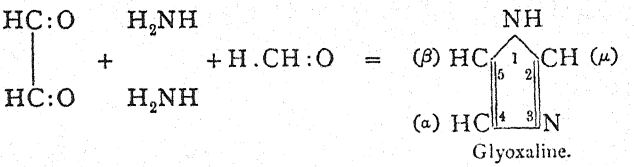
A large number of indazoles substituted in the benzene nucleus have been prepared by this method, by starting from substituted *o*-toluene-diazo-hydroxides. The diazo-compounds prepared from nitrated and brominated *o*-toluidines have a strong tendency to form rings of this type.

[1] *Ann.*, 1937, **527**, 291. [2] Barclay, Campbell and Dodds, *J. C. S.*, 1941, 113.

II.—IMINAZOLE OR GLYOXALINE GROUP

The ring system of the iminazoles, like that of the pyrazoles, consists of three carbon and two nitrogen atoms. In this case, however, the latter are not adjacent but are separated by a carbon atom. Hence iminazoles may be regarded as cyclic amidines, derived from the complex $HN{=}CH{-}NH_2$.

Iminazole, the parent compound of the series, is formed, as described on p. 253, by the action of ammonia on glyoxal, and hence is also known as **glyoxaline.** In this reaction it is assumed that a part of the glyoxal is first broken up to give formic acid and formaldehyde, and that the latter then condenses with the ammonia and glyoxal:



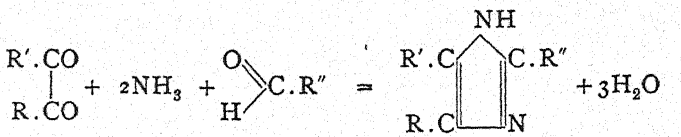
Glyoxaline.

The figures or letters attached to the formula indicate the manner in which substituents are represented.

The above is a somewhat troublesome method of preparing glyoxaline, and it is more convenient to allow formaldehyde and excess of ammonia to interact with dinitro-tartaric acid, when a good yield of ammonium glyoxaline-dicarboxylate is obtained, from which by addition of hydrochloric acid free *glyoxaline-dicarboxylic acid* is precipitated. On heating this to about 300° it decomposes smoothly into carbon dioxide and glyoxaline.

Glyoxaline forms prisms, m.p. 88° to 89° and b.p. 255°. It is a weak base, and when warm possesses a faint fishy smell.

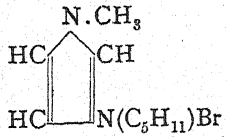
Substituted glyoxalines are prepared by a method analogous to that employed for glyoxaline, by the action of ammonia and aldehydes on glyoxal or other 1 : 2-diketo compounds.



Properties of the Glyoxalines.—Glyoxalines are stronger bases than the isomeric pyrazoles, as may be seen from their basic constants (glyoxaline $1{\cdot}2\times10^{-7}$, pyrazole $3{\cdot}0\times10^{-12}$).

The imino-hydrogen atom of glyoxaline can be replaced by metals and alkyl radicals. Ammoniacal silver solutions yield with glyoxaline a flocculent precipitate of the silver salt, which is only slightly soluble in excess of ammonia. The parent glyoxaline bases are quite stable towards alkalis, but this property is lost in the methiodides and similar derivatives,

which on heating with alkalis decompose into a mixture of two primary bases,[1] *e.g.*,



Methylglyoxaline-amylbromide

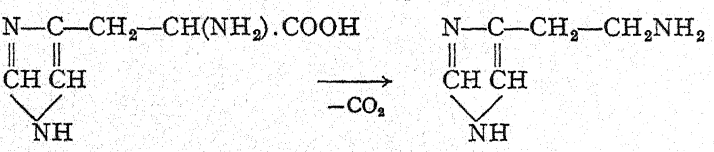
$\longrightarrow$ $H_2N.CH_3 + H_2N.C_5H_{11}$

Methylamine Amylamine.

Glyoxaline and its simple substitution products in which the imino-group is still intact are very readily disrupted, even at 0°, by a mixture of benzoyl chloride and caustic soda, with the production of a carboxylic acid and a dibenzoylated base.[2] Benzene diazo-chloride also reacts with glyoxalines containing a free imino-hydrogen atom, to yield coloured diazo-amino-compounds.[3]

Occurrence of Glyoxalines in Nature.—It has been shown by Pinner that the alkaloid *pilocarpine*, present in jaborandi leaves (of *Pilocarpus pennatifolius*), is a derivative of N-methyl-glyoxaline. Other naturally occurring iminazole derivatives, such as caffeine, theobromine and theophylline, have already been described under the purine group. The purines, in fact, contain a nucleus formed by the fusion of an iminazole ring with a pyrimidine ring. Iminazole derivatives are also met with among the disruption products of proteins (see Histidine). The discovery of a remarkable transformation from the sugars to the iminazole group (see p. 305) lends additional interest to this series from the physiological as well as the chemical standpoint.

β-Iminazyl-ethylamine, *histamine*, is of biochemical interest. It is formed from histidine by bacterial putrefaction, and can therefore be isolated from the putrefaction products of proteins.



Histidine Histamine.

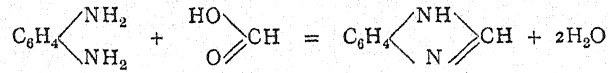
It is found in the fresh mucous membrane of the small intestine; and is also present in preparations of ergot, where it is of importance in connection with the activity of the drug, as it causes contraction of the muscles of the uterus. The base has been prepared synthetically.[4] Its hydrochloride crystallises from alcohol in prisms, m.p. 240°.

4(5)-Nitro-iminazole-5(4)-carboxylic acid has been obtained by the oxidative disruption of protein by means of nitric acid. It is readily prepared in the following stages: 4(5)-*methyl-iminazole* → 5(4)-*nitro*-4(5)-*methyl-iminazole* → *carboxylic acid*.[5]

[1] Pinner and Schwarz, *Ber.*, 1902, 35, 2441. [2] According to recent investigations of Oddo and Mingoia (*Gazzetta*, 1926, 56, 958) this statement is incorrect, the product of the reaction being benzoyl-glyoxaline. [3] Burian, *Ber.*, 1904, 37, 696. [4] *Ber.*, 1907, 40, 3691. Windaus and Opitz, *Ber.*, 1911, 44, 1721. [5] A. Windaus and W. Langenbeck, *Ber.*, 1923, 56, 683.

Benziminazoles or Benzo-glyoxalines

These compounds contain a condensed glyoxaline-benzene structure, and bear to the glyoxalines the same relationship as the indoles to the pyrroles. They are cyclic *o*-amidines of the benzene series, and are formed by the condensation of *o*-phenylene diamine and its substitution products with carboxylic acids or their anhydrides, *e.g.*,



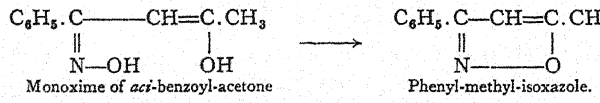
Benziminazole, *o-phenylene-formamidine*, is obtained by the above method and also by the interaction of chloroform, potassium hydroxide, and *o*-phenylene diamine. It crystallises in colourless needles of melting-point 170°.

The basic character of the benziminazoles is not quite so marked as that of the glyoxalines. They are also weakly acidic and generally soluble in aqueous alkalis with the formation of N-metallic compounds. Like the glyoxalines they are attacked by benzoyl chloride and caustic soda, yielding dibenzoylated *o*-diamines. Towards oxidising and reducing agents they are very stable.

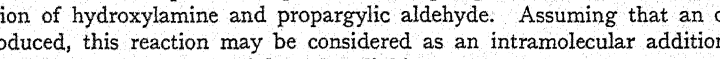
III.—ISOXAZOLES, OXAZOLES AND THIAZOLES

In those rings composed of three carbon atoms linked with one nitrogen and one oxygen atom, nitrogen and oxygen may be adjacent or separated by an atom of carbon. In the former case the compounds are termed *isoxazoles* and in the latter *oxazoles.*

Isoxazoles correspond to pyrazoles, and just as the latter are obtained from hydrazones, the former result by loss of water from the monoximes of β-diketones and β-ketoaldehydes, *e.g.*,

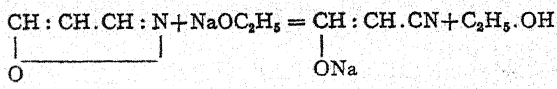


They are also produced by the action of red fuming nitric acid on diketones and esters of ketonic acids.[1] The parent compound of this group, **isoxazole,** is obtained by the interaction of hydroxylamine and propargylic aldehyde. Assuming that an oxime is first produced, this reaction may be considered as an intramolecular addition of the oximino-group, N.OH, to the triple carbon linking :



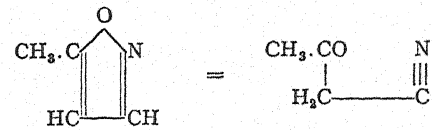
Isoxazole is a clear, mobile liquid, with a penetrating smell resembling that of pyridine ; it boils at 95·5°. Isoxazoles, like pyrazoles, are weak bases.

On being mixed with an alcoholic solution of sodium ethoxide, isoxazole decomposes to give the sodium salt of cyano-acetaldehyde or cyano-vinyl alcohol :



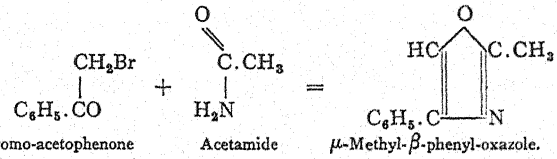
[1] J. Schmidt and Wiedmann, *Ber.*, 1909, **42**, 1869.

In an analogous manner α-alkyl-isoxazoles, in which the γ-position is unsubstituted, are attacked comparatively rapidly by alkalis and instantaneously by sodium ethoxide, forming salts of the isomeric cyano-ketones, *e.g.*,



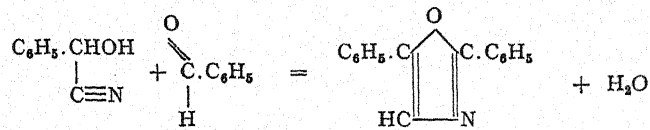
On the other hand, α : γ-dialkyl-isoxazoles are extremely stable towards alkalis.

Oxazoles correspond to glyoxalines or iminazoles. A general method for their preparation is by the interaction of acid amides with α-halogen-substituted ketones,



Bromo-acetophenone — Acetamide — μ-Methyl-β-phenyl-oxazole.

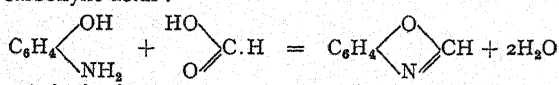
or by the action of cyanhydrins of aromatic aldehydes on the aldehydes themselves.[1]



Benzaldehyde cyanhydrin — α, μ-Diphenyl-oxazole.

The oxazoles are weak bases, and in many cases the ring is comparatively easily ruptured. Oxazole itself, the simplest member of the group, has not yet been prepared.

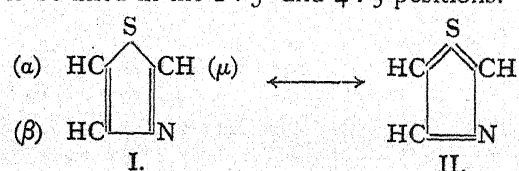
The **benzoxazoles** may be compared to the benziminazoles. Just as the latter are obtained from *o*-diamino-benzenes, the former result from *o*-aminophenols by condensation with carboxylic acids :



o-Aminophenol — Benzoxazole (m.p. 30.5°, b.p. 182.5°).

Benzoxazoles possess a weak basic character, and on being heated with hydrochloric acid decompose into their components—aminophenols and carboxylic acids.

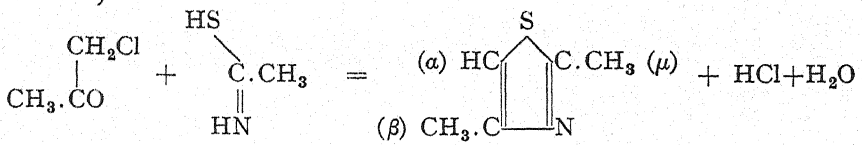
Thiazole stands in the same relationship to pyridine as thiophene does to benzene. As has already been shown on pp. 625, 627, the last two compounds possess many properties in common and a similar resemblance exists between thiazole and pyridine. Thiazole is usually represented as in I, although recent work by Erlenmeyer [2] indicates that it is more correctly regarded as a resonance hybrid of I and II. This formulation is in better agreement with the behaviour of the sulphur atom, which is not that of divalent sulphur, and with the fact that the double bonds do not appear to be fixed in the 2 : 3- and 4 : 5-positions.



I. II.

[1] E. Fischer, *Ber.*, 1896, **29**, 207. [2] H. Erlenmeyer and co-workers, *Helv. chim. Acta*, 1938, **21**, 863, 1017.

Thiazoles are formed by the interaction of thioamides and α-chloro-ketones or α-chloro-aldehydes.[1] (Compare method given above for oxazoles.)

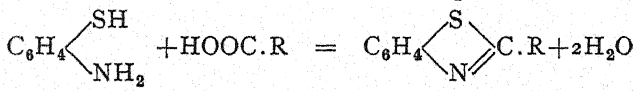


Chloracetone Thioacetamide β, μ-Dimethyl-thiazole.

If thiourea is used in this reaction μ-amino-thiazoles are formed, which on treatment with nitrous acid and alcohol exchange the amino-group for hydrogen, with the production of thiazoles.

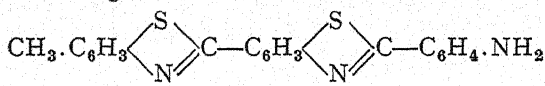
Thiazole itself is prepared by the above method from μ-amino-thiazole, and forms a mobile, volatile liquid, boiling at 117°, with a smell like pyridine. It is less basic than the latter. A large number of derivatives of thiazole are known, which cannot be described here.

Benzo-thiazoles resemble the quinoline bases, and correspond in their composition to the benzoxazoles and benziminazoles. They are produced by the action of acids on *o*-amino-thiophenols.



Certain derivatives of this group are of value as substantive cotton dyes.

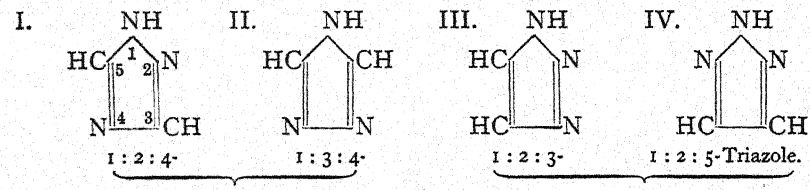
Thus when *p*-toluidine and sulphur are heated together for a considerable time at 200°, a product known as "**primuline base**" is obtained, containing the following thiazole derivative,



This is readily sulphonated to give **primuline,** which dyes cotton a yellow colour without the aid of mordants.

IV.—TRIAZOLES OR PYRRODIAZOLES

If two of the CH-groups in pyrrole are replaced by two N-atoms, four different ring systems may be derived, as represented by the following formulæ :

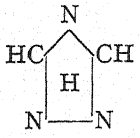


1 : 2 : 4- 1 : 3 : 4- 1 : 2 : 3- 1 : 2 : 5-Triazole.

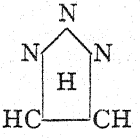
In this series we meet with tautomeric phenomena recalling those described under pyrazole (see pp. 655 *et seq.*). Whereas all four compounds are known in the form of their N-alkyl and N-aryl derivatives,

[1] Hantzsch, *Ann.*, 250, 257.

the parent substance I appears to be identical with II, and similarly III with IV. For this reason it is convenient to make use of the following formulæ :



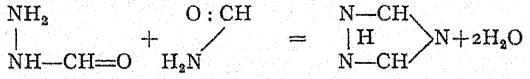
sym-Triazole



v-Triazole, osotriazole.

in which the position of the mobile hydrogen atom is not specified.

Sym-**Triazole** is obtained by various reactions, *e.g.* by the condensation of formyl-hydrazide with formamide :



and also by the action of nitrous acid on hydro-tetrazine.[1] This last reaction is of interest as illustrating the conversion of a six- into a five-membered ring :

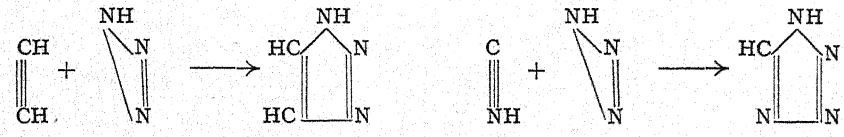
Both these methods are of general application, and symmetrical or true triazoles can therefore be prepared :

1. From dihydro-tetrazines.[2]

2. By the action of acid hydrazides on amides. Instead of starting from the hydrazide itself, the hydrazine hydrochloride may be heated with two molecular proportions of the amide. In this case ammonia is first liberated with the formation of a hydrazide, which then acts upon the second molecule of amide.

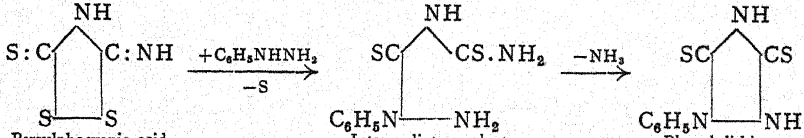
3. By warming the acid derivatives known as hydrazidines (Pinner[3]).

1 : 2 : 3-Triazole is formed by the union of acetylene and hydrazoic acid. The latter also unites with hydrogen cyanide, forming tetrazole.[4]



Phenylazide, $C_6H_5N_3$, and sodium ethoxide in boiling alcoholic solution give 1-phenyl-1 : 2 : 3-triazole (m.p. 56°) as the main product of reaction.[5] The use of diazobenzene-imide and higher alkoxides leads in general to the formation of 4-alkyl-1-phenyl-1 : 2 : 3-triazoles.

Sulphur derivatives of triazole are produced by the action of phenyl-hydrazine on persulphocyanic acid.[6]



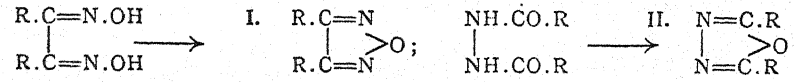
Persulphocyanic acid — Intermediate product — Phenyl-dithio-triazolidone.

[1] Hantzsch and Silberrad, *Ber.*, 1900, **33**, 58. [2] Busch and Heinrichs, *Ber.*, 1900, **33**, 455. [3] Pinner, *Ann.*, **297**, 221 ; 1898, **298**, 1. [4] O. Dimroth and co-workers, *Ber.*, 1910, **43**, 2219, 2899. [5] A. Bertho, *Ber.*, 1925, **58**, 859. [6] Fromm and co-workers, *Ann.*, 1906, **348**, 174 ; *Ber.*, 1923, **56**, 1370.

Triazole sublimes in needles, m.p. 120° to 121° and b.p. 260° (100° under 0·1 mm. pressure). It is a weak base ($K=2\cdot2\times10^{-12}$) but yields metallic salts, *e.g.* $(C_2H_2N_3)_2Cu$.

In general, the triazoles closely resemble the pyrazoles in behaviour, but are even more stable towards oxidising agents. They are all very weak bases, although the introduction of two methyl or ethyl groups somewhat increases the basic strength. As in the case of the pyrazoles, a number of interesting tautomeric phenomena have been discovered among the 1 : 2 : 3-triazoles.[1]

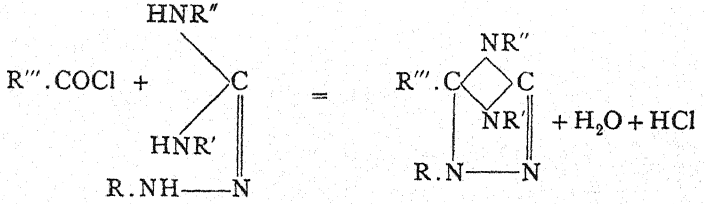
Other ring compounds of similar type are the **furazanes** (I), resulting from the oximes of α-diketones by removal of water, and the **oxydiazoles** (II), obtained from symmetrical diacyl-hydrazines.



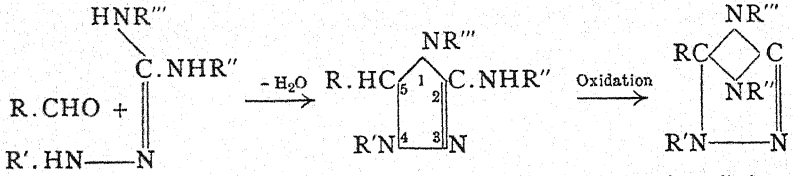
Endimino-triazoles

Peculiar triazole bases containing a "nitrogen bridge," and known as endimino-triazoles, have been prepared by Busch.[2] They are produced :

1. From acid chlorides and triarylamino-guanidines,



2. By condensing aldehydes with triarylamino-guanidines and oxidising the resulting products.



1:4:5-Trialkyl-3-alkylamino-dihydro-triazole

An endimino-triazole.

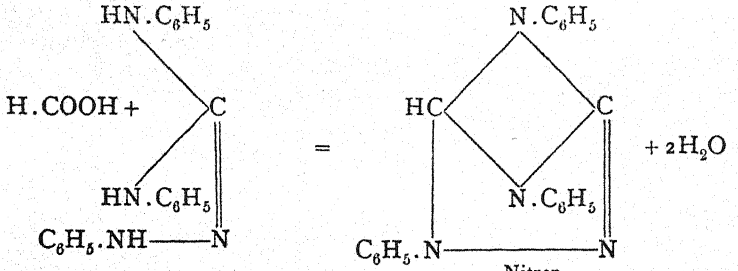
Most of the endimino-triazoles are yellow compounds, which possess strong basic character and crystallise well. Although very stable towards acids, they are readily decomposed into their original components by alkalis.

Endimino-triazoles are also of practical interest in so far as their nitrates are much more sparingly soluble than any other nitrates yet examined, so that these bases may be employed as a reagent for the nitrate ion.

The nitrate of **1 : 4-diphenyl-endanilo-dihydro-triazole** is the least soluble of these compounds and may be used successfully for the *qualitative* and also the *quantitative estimation of nitric acid*. For this reason the base has been termed **nitron.**

[1] Dimroth, *Ann.*, 1909, **364**, 183. [2] M. Busch, *Ber.*, 1905, **38**, 856, 861, 4049.

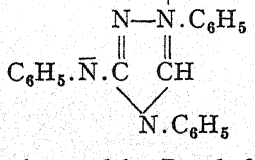
Nitron is prepared from triphenyl-aminoguanidine and formic acid, according to the following equation :



Nitron,
1:4-Diphenyl-3:5-endanilo-dihydro-triazole.

It crystallises in yellow leaflets or plates which melt with decomposition at 189°.

As a reagent, a 10 per cent. solution of nitron in 5 per cent. acetic acid is used. About 5 to 6 c.c. of the liquid under examination are acidified with one drop of dilute sulphuric acid, and five to six drops of the nitron solution added. In the presence of nitric acid a voluminous white precipitate immediately separates, and by this means nitric acid may be detected even at a dilution of 1 in 60,000. Nitron may also be employed for the detection and estimation of nitrates in the presence of nitrites.[1]

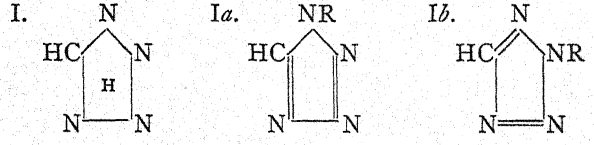


Schönberg [2] has pointed out that the structures advanced by Busch for the above compounds are very improbable owing to the distortion of the normal valency angles of the carbon joining the double bond to the four-membered ring. He suggests the annexed formula for nitron.

V.—TETRAZOLES

Tetrazoles contain a ring system built up from one carbon and four nitrogen atoms.

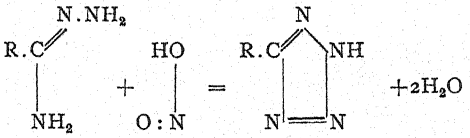
Once again tautomeric phenomena are observed, similar to those described in the case of pyrazole and triazole, the one parent compound (I) giving rise to two series of derivatives (I*a* and I*b*) :



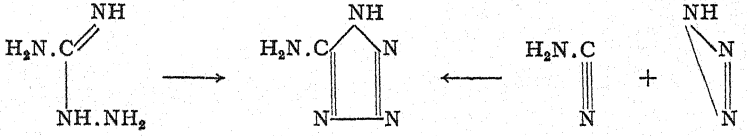
Owing to the mobility of the double bonds, the hydrogen compounds corresponding to the types I*a* and I*b* are in a state of dynamic equilibrium with one another, and isomerism can only be detected if intramolecular change is retarded by substituting the imino-hydrogen atoms.[3]

[1] M. Busch, *Ber.*, 1905, **38**, 863. For the determination of nitric acid in water see Busch, *J. C. S.*, A, 1905, ii., 418. [2] A. Schönberg, *J. C. S.*, 1938, 824. [3] Wedekind, *Ber.*, 1896, **29**, 1846. M. Freund, *Ber.*, 1901, 34, 3110.

Tetrazoles are formed by various reactions, *e.g.* with great readiness from nitrous acid and hydrazidines :



An arrangement of atoms similar to that in the hydrazines is present in amino-guanidine. The latter on treatment with nitrous acid yields amino-tetrazole, which is also formed by the addition of cyanamide to hydrazoic acid.



Tetrazole may be obtained from amino-tetrazole by way of the diazo-compound in the same manner as benzene is obtained from aniline.

For the formation of tetrazole from hydrazoic acid see p. 666, and for the synthesis of tetrazoles from diazobenzene-imide see O. Dimroth and Merzbacher, *Ber.*, 1907, **40**, 2402.

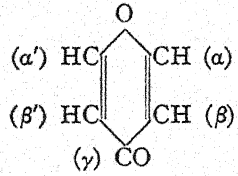
The tetrazole ring is very similar in nature to the benzene ring. Those tetrazoles containing a free imino-group are strong monobasic acids. The silver and copper salts of tetrazoles explode with violence on heating.

Tetrazole forms colourless crystals of melting-point 156°, and its aqueous solution is acid in reaction. It possesses no basic properties and gives no nitroso-derivative.

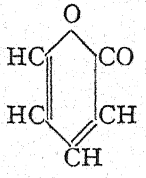
IV

Pyrones

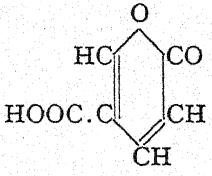
The pyrone ring contains five carbon atoms and one oxygen atom, and according to their arrangement a distinction is drawn between γ-pyrones and α-pyrones.



γ-Pyrone
m.p. 32°, b.p. 315°



α-Pyrone
b.p. 206-209°



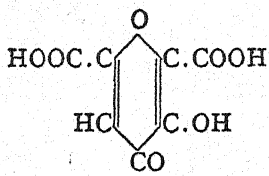
Coumalic acid.

Benzo-derivatives of α-pyrone have already been described on p. 458, under *coumarins*, the γ-lactones of unsaturated aliphatic-aromatic *o*-hydroxy acids. A simple derivative of α-pyrone is *coumalic acid* (coumalinic acid), which can be prepared from malic acid (see p. 281). In the following pages will be found a description of the *γ-pyrones, generally known as pyrones*.

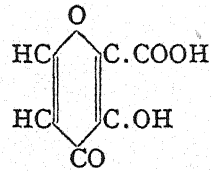
γ-PYRONES

γ-Pyrone is the parent compound of a series of substances found in nature, *e.g. brazilin*,[1] the colouring matter of red-wood, and in recent years the pyrones have also attracted interest in connection with investigations on the basic properties of oxygen.

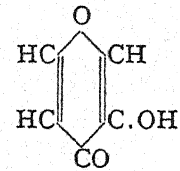
A naturally occurring derivative of γ-pyrone is the **meconic acid** present in opium. On being heated, this acid parts with carbon dioxide to form *comenic acid* and finally *pyromeconic acid* (also known as pyrocomenic acid).



Meconic acid, β-hydroxy-pyrone-α α′-dicarboxylic acid

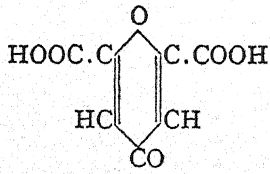


Comenic acid, β-hydroxy-pyrone-α-carboxylic acid

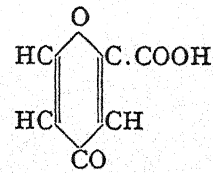


Pyromeconic acid, β-hydroxy-γ-pyrone (m.p. 121°).

Another compound of the same type is **chelidonic acid**, found in the celandine and white hellebore. On being heated, this yields *comanic acid* and then pyrone.

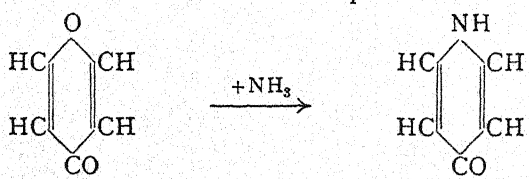


Chelidonic acid, pyrone-α α′-dicarboxylic acid (m.p. 262°)



Comanic acid, pyrone-α-carboxylic acid (m.p. 250° with decomp.).

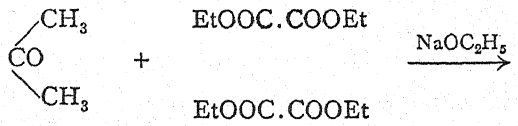
The close relationship existing between the pyrones and pyridones is at once visible on comparing the formulæ of these two series of compounds, and is also confirmed by experiment, since the pyrones on treatment with ammonia are readily converted into the corresponding pyridones. In this change the ring oxygen atom is replaced by the NH-group, and it has been suggested that various alkaloids derived from pyridine are synthesised in this manner in the tissues of plants.

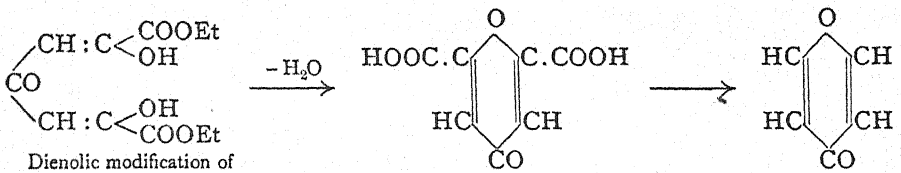


γ-Pyrone γ-Pyridone.

[1] See Crabtree and R. Robinson. *J. C. S.*, 1918, **113**, 872. W. H. Perkin, J. N. Rây, and R. Robinson, *J. C. S.*, 1927, 2094. P. Pfeiffer and co-workers, *Ber.*, 1924, **57**, 208; 1927, **60**, 2142; 1928, **61**, 839.

The *synthesis of chelidonic acid and pyrone* may be effected from acetone-dioxalic ester. The latter is obtained by condensing acetone with two molecules of oxalic ester, and very readily loses water—even when boiled in alcoholic solution—to form chelidonic ester. When acetone-dioxalic ester is heated with hydrochloric acid, loss of water and hydrolysis take place simultaneously, with direct production of chelidonic acid. Pyrone may be obtained from chelidonic acid by dry distillation, preferably with the addition of copper powder.





Dienolic modification of acetone-dioxalic ester

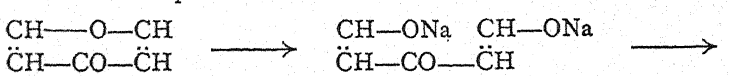
Chelidonic acid

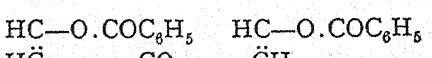
Pyrone.

Chelidonic acid and pyrone are readily disrupted to give open-chain compounds. On being boiled with alkali, the former decomposes smoothly into 1 mol. acetone and 2 mols. oxalic acid,

$$C_7H_4O_6+3H_2O = 2HO_2C.CO_2H+CH_3.CO.CH_3.$$

Pyrone is easily converted into derivatives of bis-*hydroxymethylene-acetone*.[1] Even a short treatment with alkali in the cold is sufficient to bring about this change. The reaction may be conveniently followed by adding benzoyl chloride to the alkaline liquid, when the bis-hydroxymethylene-acetone separates out in the form of its dibenzoate.





Dibenzoate of *bis*-hydroxymethylene-acetone.

Owing to its insolubility this dibenzoyl compound provides a useful means of testing for pyrone itself in dilute aqueous solution.

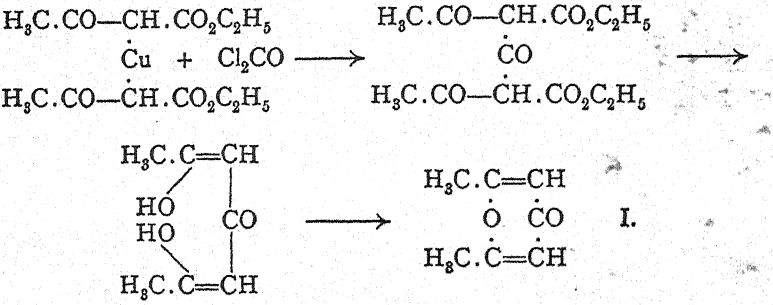
A similar opening of the pyrone ring is produced by the action of aniline acetate, when the dianilide of bis-hydroxymethylene-acetone is formed.[2]

Salt Formation with Dimethyl-pyrone and Pyrone, and the Tetravalency of Oxygen

Dimethyl-pyrone (I), m.p. 132° and b.p. 248°, has been used by Collie and Tickle[3] as the basis of an investigation into the tetravalency of oxygen. It may be prepared by condensing the copper salt of aceto-acetic

[1] Willstätter and Pummerer, *Ber.*, 1904, **37**, 3734, 3744; **38**, 1465. [2] W. Borsche and Bonacker, *Ber.*, 1921, **54**, 2678. [3] Collie and Tickle, *J. C. S.*, 1904, **85**, 971.

ester with phosgene, and boiling the product so obtained with sulphuric or hydrochloric acid [1]:

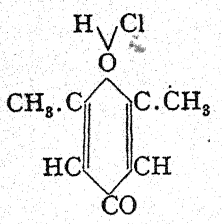


In the research quoted above, Collie and Tickle showed that dimethyl-pyrone forms addition products with a number of acids, such as $C_7H_8O_2$, HCl with hydrochloric acid; $(C_7H_8O_2)_2$, H_2PtCl_6 with hydrochloroplatinic acid; and $(C_7H_8O_2)_2$, $C_4H_6O_6$ with tartaric acid. It will be seen that these all result from the direct addition of acid, without loss of water.

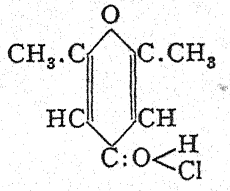
The stability and behaviour of these compounds can be explained on the assumption of a tetravalent oxygen atom with basic properties. It therefore appears that oxygen can take the place of sulphur, phosphorus and nitrogen in bases, to form derivatives of a hypothetical base, which is known as *oxonium hydroxide*, $H_3O.OH$, by analogy with the hypothetical bases: $NH_4.OH$, $PH_4.OH$, $H_3S.OH$, $H_2I.OH$. Salts of this oxygen base are known as **oxonium salts.**[2]

In this connection it will be seen that dimethyl-pyrone contains two oxygen atoms, leading to the possibility of either of the formulæ I*a* or I*b*

I*a*.



I*b*.



for dimethyl-pyrone salts. So far it has not been found possible to decide with certainty between these two types, although the structure I*b* seems the more probable. Experience shows that the carbonyl oxygen possesses more free affinity than the oxygen of ethers.

An examination of the electrical conductivity of dimethyl-pyrone salts in aqueous solution indicates that they are almost completely hydrolysed. Dimethyl-pyrone also unites with methyl sulphate to give an addition product, which on treatment with potassium iodide yields dimethyl-pyrone methiodide, of the composition CH_3I+dimethyl-pyrone.

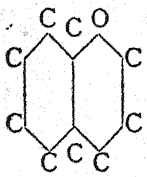
[1] F. Feist, *Ann.*, 1890, **257**, 253. Willstätter and Pummerer, *Ber.*, 1905, **38**, 1465. [2] See also J. Kendall, *J. Am. C. S.*, 1917, **39**, 2303; and Knox and Richards, *J. C. S.*, 1919, **115**, 508.

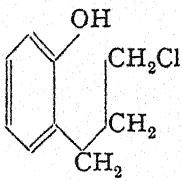
Salts are also formed by the parent compound pyrone (*e.g.* hydrochloride, picrate and oxalate), but in this case there is a strong tendency towards the formation of more complex salts.[1] Pyrone combines, in addition, with inorganic salts such as calcium chloride, mercuric chloride and silver nitrate. In this respect it resembles the amino-acids, in which Strecker assumes that the carbonyl group binds the metallic radical, and the amino-group the acidic radical of the salts. This would point to the tetravalent oxygen of pyrone possessing both basic and acidic character, and is in agreement with Walden's assumption—based on conductivity experiments—that dimethyl-pyrone is an *amphoteric electrolyte*.[2]

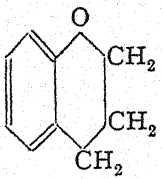
The discovery of the salts of dimethyl-pyrone, and their formulation as oxonium salts, has stimulated research into the question as to whether salt formation is a property of oxygen compounds in general. Experimental results obtained by Baeyer and Villiger[3] indicate that this is the case, and in recent years evidence has been supplied by other investigators confirming the existence of a great variety of addition compounds, which are regarded as salts of tetravalent oxygen[4] (see pp. 137, 160, and 576).

BENZO- AND DIBENZO-γ-PYRONE

The cyclic oxide chromane (formula III below) may be regarded as the parent compound of a number of derivatives such as the chromones and coumarins, containing the atomic framework (I). **Chromane** has been

I. 

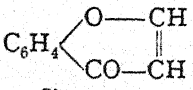
II. 

III. 

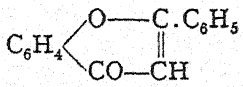
prepared from the base tetrahydro-quinoline[5] (see p. 697). The nitrogen ring of the latter may be opened to give *o*-γ-chloropropyl-aniline, which by means of the diazo-reaction can be converted into *o*-γ-chloropropyl-phenol (II). In alkaline solution this is quantitatively transformed into chromane.

Chromane is a strongly refractive liquid, which smells like peppermint and boils at 214° to 215° (749 mm. press.). It dissolves in concentrated sulphuric acid, giving a pink solution.

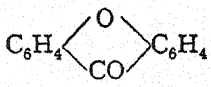
From benzopyrone (*chromone*) and dibenzopyrone (*xanthone*) are derived a number of naturally occurring yellow dyes, the colour of which is due to the chromophore CO.



Chromone,
benzo-γ-pyrone



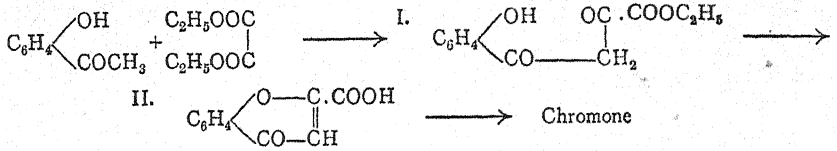
Flavone,
β-phenyl-benzo-γ-pyrone



Xanthone,
dibenzo-γ-pyrone.

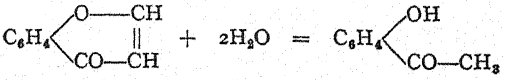
[1] A. Werner, *Ann.*, 1902, **322**, 296. Willstätter and Pummerer, *Ber.*, 1904, **37**, 3740. [2] *Ber.*, 1901, **34**, 4185; 1902, **35**, 1764. [3] Baeyer and Villiger, *Ber.*, 1901, **34**, 2679. [4] See Knox and Richards, *J. C. S.*, 1919, **115**, 508, and J. Kendall, *J. Am. C. S.*, 1917, **39**, 2303. [5] Braun and Steindorff, *Ber.*, 1905, **38**, 850.

Chromone can be synthesised from *o*-hydroxy-acetophenone and oxalic ester.[1] In the presence of sodium these react with one another to form *o*-hydroxy-benzoyl-pyroracemic ester (I), which, on boiling with alcoholic hydrochloric acid, loses a molecule of water and yields chromone-carboxylic acid (II). The latter on distillation parts with carbon dioxide to form chromone. This is a general method for the preparation of chromones.

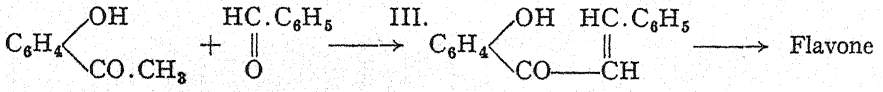


The reaction described on p. 459, for the formation of coumarin derivatives from phenols and β-ketonic esters, has been adapted to the preparation of chromones by modifying the conditions of condensation and using phosphorus pentoxide in place of sulphuric acid.[2]

Chromone forms white needles, m.p. 59°. When boiled with sodium ethoxide it decomposes into *o*-hydroxy-acetophenone and formic acid.

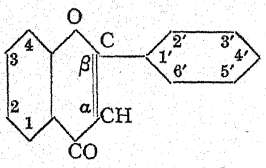


Flavone, m.p. 99° to 100°, is prepared in various ways,[3] *e.g.* *o*-hydroxy-acetophenone condenses with benzaldehyde to give hydroxy-chalkone (III), which when acetylated and converted into the di-bromide yields flavone on subsequent treatment with alcoholic potash.

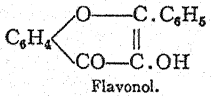


In this manner Kostanecki has synthesised a number of yellow dye-stuffs occurring in nature, all of which are mordant dyes and in general contain two hydroxyls in the *o*-position to one another.

Position isomerides are described according to the following notation proposed by Kostanecki.



Flavone.



Flavonol.

Examples of this group are :

Chrysin, 1 : 3-*dihydroxy-flavone*, $C_{15}H_{10}O_4$, a constituent of poplar buds.

Luteolin, 1 : 3 : 3′ : 4′-*tetrahydroxy-flavone*, $C_{15}H_{10}O_6+2H_2O$, the dye of *dyer's weed*, Reseda luteola. With aluminium mordant it dyes yellow, and is employed particularly for silk.

Fisetin, 3 : 3′ : 4′-trihydroxy-flavonol, isomeric with luteolin, and a hydrolysis product of the glucoside **fustin** contained in young fustic.

Quercetin, 1 : 3 : 3′ : 4′-tetrahydroxy-flavonol, $C_{15}H_{10}O_7$, a hydrolytic product of the glucoside **quercitin**, $C_{21}H_{22}O_{12}$, present in quercitron bark.

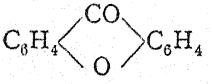
[1] Kostanecki and co-workers, *Ber.*, 1901, **34**, 2375 ; **35**, 859, 861, 2547, 2887. [2] Petschek and Simonis, *Ber.*, 1913, **46**, 2014. [3] Kostanecki and co-workers, *Ber.*, 1898, **31**, 1757 ; 1900, **33**, 330 ; 1904, **37**, 2634. Ghosh, *J. C. S.*, 1916, **109**, 105.

Rhamnetin, methyl-quercetin, a hydrolysis product of the glucoside **xantho-rhamin** contained in Avignon berries and buckthorn berries.

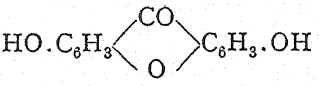
Morin, isomeric with quercetin, a constituent of the wood of *Morus tinctoria* ("fustic"). Used in the form of an extract, particularly for dyeing wool.

Finally we may mention **apigenin,**[1] or 1 : 3 : 4′-*trihydroxy-flavone*, obtained by the hydrolysis of the glucoside *apiin*, which occurs in parsley and to a smaller extent in celery.

Xanthone can be prepared by the elimination of water from phenyl-salicylic acid. The most interesting of its derivatives is euxanthone.



Xanthone,
m.p. 174°, b.p. 250°.

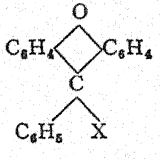


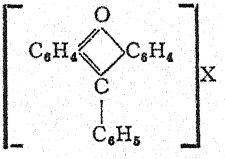
Euxanthone, dihydroxy-xanthone,
b.p. 237°.

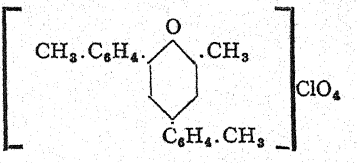
Euxanthone [2] is prepared from the natural dye-stuff *piuri* or Indian yellow, in which it occurs free and also in combination with glucuronic acid in the form of *euxanthic acid*. The magnesium salt of euxanthic acid is the chief constituent of the Indian yellow of commerce, which is used as a painter's colour.

Euxanthone can be synthesised from hydroquinone-carboxylic acid and resorcinol : the reaction is a general one, and by condensing hydroxy-acids with polyhydric phenols numerous xanthone derivatives can be prepared. Up to the present, however, these are without practical value.

Xanthylium and Pyrylium Salts.—Xanthylium salts stand in close relationship to the triarylmethylium salts already discussed on pp. 509 *et seq.* They only differ from the latter in containing an oxygen bridge between two of the benzene nuclei, and hence the two classes of compounds have very similar properties. Gomberg and Cone showed that the xanthyl halogenides, although colourless, yield coloured products by further addition of salts or acids. The xanthylium compounds formed with oxygen-acids, however, are without exception coloured. In these respects there is a complete resemblance to the triarylmethane derivatives. Kehrmann [3] found that in certain special cases even the simple halogenides of the xanthyl series may be coloured and then also possess the character of salts. By analogy with the triaryl compounds the colourless xanthyl derivatives are formulated as in I, the coloured salt-like compounds as in II.

I. 

II. 

III. 

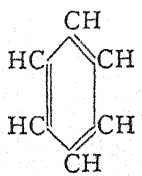
The xanthylium salts are closely related to the *benzopyrylium salts*, occurring in the anthocyanidin colouring matters of plants and berries (pp. 827 *et seq.*), and to the simple *pyrylium salts* [4] (III), which may be regarded as the parent compounds of the whole group.

[1] Kostanecki, *Ber.*, 1900, **33**, 1988. Vongerichten, *Ber.*, 1900, **33**, 2334. *Ann.*, 1901, **318**, 121.
[2] For a synthesis see Ullmann and Panchaud, *Ann.*, 1906, **350**, 108. [3] F. Kehrmann, *Ann.*, 1910, **372**, 287. [4] W. Dilthey and co-workers, *Ber.*, 1923, **56**, 1012 ; 1924, **57**, 1653. Also O. Diels and K. Alder, *Ber.*, 1927, **60**, 716.

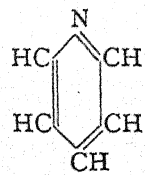
V

Pyridine Group

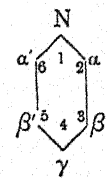
Pyridine and its derivatives contain a ring composed of five carbon atoms and one nitrogen atom. Pyridine can therefore be derived from benzene by replacing a trivalent CH-group by an atom of nitrogen. It is the parent compound of a number of vegetable alkaloids.



Benzene



Pyridine.



The above formula, proposed by Körner in 1869, offers a satisfactory explanation of the chemical behaviour of pyridine and its derivatives, and of the well-marked analogy between benzene and pyridine. It has been confirmed by several syntheses of pyridine compounds. As in the case of benzene, other formulæ have also been put forward.

The *possibilities of isomerism* among derivatives of pyridine are greater than with benzene, since not only does the relative position of the constituents to one another enter into the question, but also their position with regard to the nitrogen of the ring. Isomerides are usually described by the use of numbers or letters, as indicated in the above formulæ. Theory predicts the existence of three monosubstitution products, and six or twelve disubstitution products, according as the substituents are similar or dissimilar.

Preparation, Properties and Uses of Pyridine.—Pyridine and certain of its homologues are produced by the action of heat on coal, peat, wood and various bituminous shales, and are thus present in the tar obtained by the dry distillation of these substances. They also occur in the unpleasant smelling product known as Dippel's oil, formed by the dry distillation of bones from which the fat has not been extracted. As will be seen later, pyridine results from various alkaloids by the action of heat or alkalis, or by distillation with zinc dust at a red heat.

At present the chief source of pyridine and its homologues is coal tar. The fraction of the tar boiling between 80° and 170° ("light oil," see p. 378) used for the production of benzol is also worked up for pyridine bases, which are present to the extent of several units per cent. The oil is washed with dilute sulphuric acid in lead-lined vessels, and the bases are then liberated from the acid solution by addition of lime, and purified by rectification. The mixture of pyridine bases so obtained is used industrially in denaturing spirits, and as a solvent in the purification of crude anthracene (see p. 549).

Pyridine is a colourless liquid of unpleasant, penetrating smell, b.p. 114·5° and sp. gr. 1·0033 at 0°. It is miscible in all proportions with water, alcohol and ether, and forms salts with acids. Among the latter, the *ferrocyanide* and the *perchlorate* [1] are difficultly soluble and are used for the isolation and purification of pyridine.

The outstanding feature of pyridine is its great stability. Chromic acid, potassium permanganate and nitric acid do not attack it, and with sulphuric acid it is only converted into a sulphonic derivative at about 300°. Halogen-substitution products are also only obtained with great difficulty, the halogen entering the β-position; mercuration, on the other hand, proceeds readily.[2] Pyridine is a tertiary base, and when reduced with sodium and alcohol yields the secondary base, piperidine.

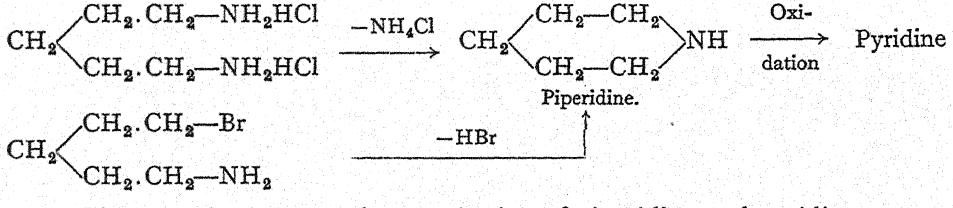
Pyridine sulphuric anhydride is prepared as a crystalline compound by drawing carefully regulated currents of air, impregnated respectively with sulphur trioxide (from warm oleum) and pyridine, into a barrel-shaped receiver. The product is used for the preparation of sulphuric esters of phenolic compounds, in place of the mixture of chlorosulphonic acid and pyridine previously employed. It is much less sensitive to moisture than the usual sulphonating agents, and as a solid is more easily handled and weighed. The addition compound formed from pyridine and sodium pyrosulphate may be used in a similar manner.

Syntheses of Pyridine and its Derivatives

1. The simplest method of building up a pyridine ring is from aliphatic compounds of the general formula

$$X—CH_2.CH_2.CH_2.CH_2.CH_2—NH_2$$

which may be converted into piperidine by ring formation, and by subsequent oxidation yield pyridine. Thus pentamethylene-diamine hydrochloride, on rapid heating, decomposes into ammonium chloride and piperidine. Similarly, normal ω-chloro- and ω-bromo-amylamine lose hydrogen halide on heating with alkali to give piperidine (Ladenburg).



These syntheses prove the constitution of piperidine and pyridine.

2. A pyrogenic synthesis of pyridine, analogous to that of benzene from acetylene, occurs when acetylene and hydrogen cyanide are led through a tube heated to redness.

$$2C_2H_2+CNH = C_5H_5N$$

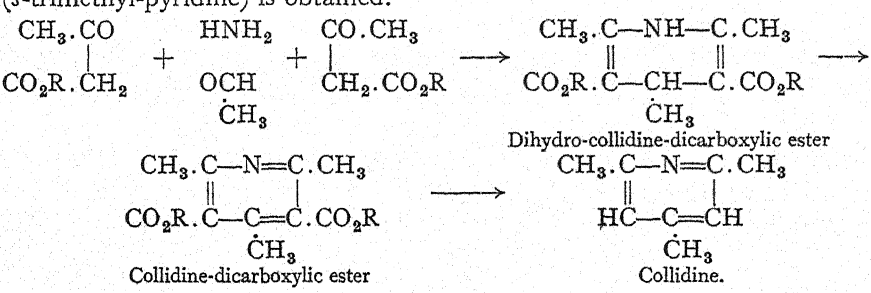
3. The formation of pyridine derivatives from those of pyrrole, by extension of the ring, has already been mentioned on p. 613.

[1] *Ber.*, 1926, 59, 1074. [2] G. Sachs and R. Eberhartinger, *Ber.*, 1923, 56, 2223.

4. Compounds of the type of aldehyde-ammonia yield alkyl pyridines when heated alone or mixed with aldehydes or ketones.

$$CH_3CHONH_3+3CH_3CHO = C_5H_3(CH_3)(C_2H_5)N+4H_2O$$

5. A synthesis of general application is due to Hantzsch. Aldehyde-ammonia unites with acetoacetic ester to form *dihydro-collidine-dicarboxylic ester*, which under the influence of nitrous acid loses two hydrogen atoms and is transformed into *collidine-dicarboxylic ester*. From this, by hydrolysis and elimination of carbon dioxide, *collidine* (*s*-trimethyl-pyridine) is obtained.[1]



It may be assumed that in the first instance one molecule of aldehyde-ammonia (or aldehyde and ammonia) reacts with two molecules of aceto-acetic ester, to form an alkylidene-acetoacetic ester and β-amino-crotonic ester, and that these compounds then interact with the production of a dihydro-pyridine derivative. In confirmation of this, it has been shown that by working at low temperatures, at which the formation of dihydro-pyridine derivatives is retarded, the presence of alkylidene-acetoacetic ester can be proved.[2]

The above reaction may be varied by using other aldehydes in place of acetaldehyde, and other 1 : 3-diketones, such as acetyl-acetone or benzoyl-acetone, instead of the second molecule of acetoacetic ester.

In addition, other reactions have been developed which permit a further extension of the above synthesis. Among these are the formation of dihydro-pyridine derivatives by condensing 1 : 5-diketones with ammonia, and alkylidene-acetoacetic esters with β-amino-crotonic ester or ammonia derivatives of 1 : 3-diketones. Alkylidene-malonic esters may also be employed in place of alkylidene-acetoacetic esters in the synthesis of pyridine compounds.[2]

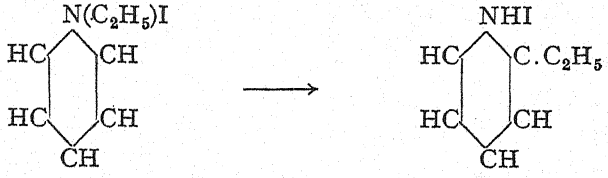
6. Pyridine derivatives can also be prepared from compounds of the pyrone group by treatment with ammonia, when the oxygen atom of the ring is replaced by the NH-group (see p. 670).

7. The intramolecular rearrangement of the alkiodides, which has already been described in the cases of aniline (p. 390), pyrrole (p. 614) and pyrazole (p. 653), was observed by Ladenburg in the pyridine group, and offers a general means of converting pyridine into its homologues.

[1] A. Hantzsch, *Ann.*, 1882, **215**, 1. *Ber.*, 1885, **18**, 2579. Compare also E. Späth and G. Bürger, *Monats.*, 1928, **49**, 265. [2] Knoevenagel, *Ber.*, 1903, **36**, 2180. Rabe and Billmann, *Ber.*, 1900, **33**, 3806.

As a tertiary base pyridine unites with alkyl iodides to form the corresponding ammonium iodides. When these are heated under pressure the alkyl radical migrates from nitrogen to a carbon atom of the nucleus, assuming either the α- or γ-position with respect to nitrogen, but never the β-position.

Thus pyridine ethiodide yields the hydriodide of ethyl pyridine :



8. Ammonia in the presence of acetic acid reacts with the oxymethylene-derivative of methyl *n*-propyl ketone to form 2-n-*propyl*-5-n-*butyryl-pyridine*, $C_5H_3(C_3H_7)(CO.C_3H_7)N$. Similarly, oxymethylene-acetone yields 2-*methyl*-5-*acetyl-pyridine*, $C_5H_3(CH_3)(COCH_3)N$.[1]

General Behaviour of Pyridine Derivatives.—The properties of pyridine itself have already been briefly described on p. 677. The parent compound and its homologues are tertiary bases, which unite with one equivalent of an acid to form salts,[2] and also combine with inorganic salts such as mercuric chloride, and the sulphates of copper, zinc and cadmium, to give double salts of the type $C_5H_5N,HgCl_2$ and $(C_5H_5N)_2$, $(HgCl_2)_3$. As was indicated on p. 652, the composition and behaviour of these addition compounds illustrate the similarity between the pyridine and pyrazole series.

Pyridine and its derivatives unite directly with sodium bisulphite. The compounds so formed readily decompose with loss of ammonia and simultaneous opening of the ring.[3]

The strong resemblance between the pyridine and benzene series is emphasised by the following facts. Oxidising agents such as nitric acid and chromic acid attack neither benzene nor pyridine. Permanganate of potash converts pyridine homologues into carboxylic acids in the same manner as benzene homologues, the side chain being oxidised while the pyridine ring remains intact. From the constitution of the pyridine-carboxylic acids so obtained, conclusions may be drawn as to the number and position of the side chains originally present. Sulphuric acid converts pyridine and its homologues into sulphonic acids, although the action is slower than with benzene. The sulphonic group in these acids can be exchanged for the hydroxyl or cyano-group, by fusion with potash or potassium cyanide respectively. The resulting hydroxy-pyridines resemble the phenols in behaviour.

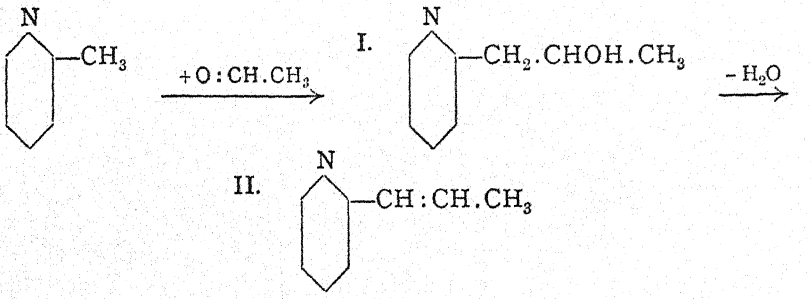
One notable difference between pyridine and benzene is that the pyridine ring can only be nitrated with great difficulty (at 300°) unless it

[1] E. Benary, *Ber.*, 1927, **60**, 914. [2] The methiodides and certain salts of pyridine and quinoline exist in modifications of different colour. The polychromism of these derivatives is ascribed to **chromo-isomerism**. Hantzsch and Hofmann, *Ber.*, 1911, **44**, 1776. Hantzsch, *ibid.*, p. 1783. [3] H. Bucherer and Schenkel, *Ber.*, 1908, **41**, 1346.

is first substituted by some group such as OH or NH_2. According to Marckwald the resistance of pyridine to nitration is due to the strongly negative character of the nitrogen atom. Thus electrophilic substituents (NO_2, Cl, Br, SO_3H) always enter the β-position in the ring, *i.e.* the *meta*-position to nitrogen. The negative character of the nitrogen atom is also revealed in the α- and γ-chloro-compounds of pyridine, the halogen of which is mobile, as in the *o*- and *p*-chloro-derivatives of nitrobenzene. The reactivity of the halogens in α- and *γ-chloro-pyridines* is shown by the conversion of these compounds into *amino-pyridines* with ammonia, *pyridyl-hydrazines* with hydrazines, and *mercaptans* with potassium hydrosulphide.

Pyridine and its homologues react with sodamide to form **α-amino-pyridines.**[1] In this case the unusual point of attack is due to the nucleophilic character of the entering substituent ($^-NH_2$). See also p. 374.

The α- and *γ-methyl-pyridines* are also unusually reactive. According to experimental conditions they either condense with aldehydes to form products of the aldol type known as *alkines*, *e.g.* compound I, or else water is eliminated and oxygen-free, unsaturated bases, such as α-allyl-pyridine (II), are produced. The latter are generally termed *stilbazoles*.[2] As will be seen later, the α-allyl-pyridine obtained by this reaction is an intermediate product in the synthesis of the alkaloid coniine. Phthalic anhydride and phthalimide may also be employed in place of aldehydes in this condensation.



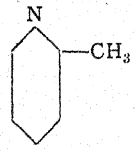
On reducing pyridine bases with sodium and alcohol, six atoms of hydrogen are taken up with formation of piperidine bases. More energetic reduction, by heating with hydrogen iodide, ruptures the ring with the production of paraffins, *e.g.* pyridine is converted into pentane.

Homologues of Pyridine

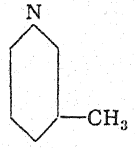
The alkyl derivatives of pyridine mentioned above are found together with pyridine itself in bone oil and coal tar.

[1] O. Seide, *Ber.*, 1924, **57**, 791. [2] Jacobsen and Reimer, *Ber.*, 1883, **16**, 1082, 2602. Ladenburg, *Ann.*, 1898, **301**, 117. Among aromatic aldehydes it appears that those substituted in the *o*-position tend to yield alkines, whereas with *m*-substitution the tendency is to the formation of stilbazoles. Bach, *Ber.*, 1901, **34**, 2229.

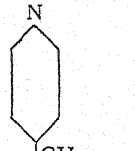
Methyl pyridines or **Picolines**, C_6H_7N. All three possible isomerides are known. They may be isolated from coal tar, or synthesised by the methods quoted above.



α-Picoline, b.p. 129°. On oxidation yields picolinic acid.



β-Picoline, b.p. 142-143°. On oxidation yields nicotinic acid.



γ-Picoline, b.p. 144-145°. On oxidation yields iso-nicotinic acid.

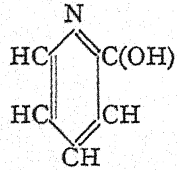
Lutidines, C_7H_9N. Nine isomerides are theoretically possible, three ethyl-pyridines and six dimethyl-pyridines. Of these, the three ethyl and five of the dimethyl-derivatives are known. *α-Ethyl-pyridine*, b.p. 184·5°, was obtained by the degradation of tropine. *β-Ethyl-pyridine*, b.p. 166°, is formed by the decomposition of quinine and its degradation products.

Collidines, $C_8H_{11}N$. No less than 22 isomerides are possible. *α-Methyl-β'-ethyl-pyridine* or *aldehydine*, b.p. 178°, is formed when aldehyde-ammonia is heated in alcoholic solution. *α-Propyl-pyridine* or *conyrine*, b.p. 166° to 168°, is closely related to the alkaloid coniine, from which it is formed on distillation with zinc dust. For *collidine*, see p. 678.

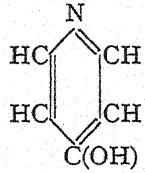
Hydroxy- and Amino-pyridines

Hydroxy-pyridines may be compared with amino-phenols, which they resemble in yielding salts with bases as well as with acids.

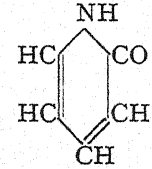
The three *hydroxy-pyridines* are high boiling substances which crystallise well. They are best prepared from the corresponding carboxylic acids by elimination of carbon dioxide, and are also formed by direct hydroxylation [1] when pyridine vapour is led over powdered potassium hydroxide at 300° to 320°. A point of special interest is the *tautomerism* exhibited by α- and *γ-hydroxy-pyridines*. Each of these reacts in two ways : as a true hydroxy-pyridine, containing a phenolic hydroxyl group, and as a **pyridone** [2] or ketonic derivative of a dihydro-pyridine.



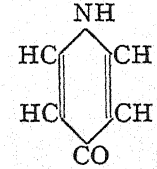
α-Hydroxy-pyridine



γ-Hydroxy-pyridine



α-Pyridone



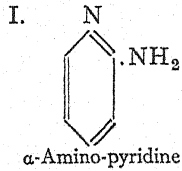
γ-Pyridone

Whereas the free α- and γ-hydroxy-pyridines have so far only been isolated in one form, and it is still uncertain whether this corresponds to the hydroxy-pyridine or the pyridone type, the alkyl ethers of these compounds each exist in two forms of the constitution $C_5H_4(OR)N$ and $C_5H_4O(NR)$ respectively. β-Hydroxy-pyridine, on the other hand, reacts only as a phenol and never according to the pyridone type.

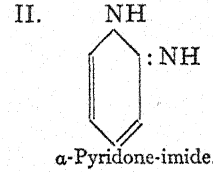
In the *di- and trihydroxy pyridines* the basic character is entirely lost. These also show tautomerism of the above kind.

[1] A. E. Tschitschibabin, *Ber.*, 1923, **56**, 1879. [2] A. E. Tschitschibabin and co-workers, *Ber.*, 1924, **57**, 1158 ; 1925, **58**, 2650. For a discussion from the standpoint of resonance see F. Arndt, *Helv. chim. Acta*, 1930, **63**, 587, 2963.

It has already been stated that pyridine reacts with sodamide to form α-amino- and αα′-diamino-pyridines. By analogy with the case of α-hydroxy-pyridine, it would be expected that α-amino-pyridine would give rise to two series of derivatives, corresponding to the tautomeric forms I and II, which may be described respectively as *α-amino-pyridine* and *α-pyridone-imide* :



α-Amino-pyridine



α-Pyridone-imide.

In actual practice alkyl derivatives of both tautomeric forms are easily prepared.[1]

A valuable antiseptic, **pyridium,** β-phenylazo-2 : 6-diaminopyridine hydrochloride, is prepared by coupling benzene diazonium chloride with 2 : 6-diaminopyridine.

Pyridine-carboxylic Acids

Carboxylic acids of the pyridine series result, as stated above, from the oxidation of pyridine derivatives containing organic side-chains. Hence they are frequently obtained as degradation products of vegetable alkaloids, and a knowledge of their constitution is of great value in investigating the structure of the latter. They are solid compounds, which possess both acidic and basic character, although the basic properties are not very evident in poly-carboxylic acids. When heated with lime, all these acids decompose into pyridine and carbon dioxide. A carboxyl group in the α-position is particularly readily removed, and α-acids also differ from the others in giving a yellowish-red coloration with ferrous salts. *Pyridine mono-carboxylic acids*, $C_5H_4(COOH)N$, have already been mentioned on p. 681.

In **picolinic acid** (sublimes at 134° to 136°) the carboxyl group has been proved to occupy the α-position,[2] and this proof is one of the foundations upon which the absolute orientation of pyridine derivatives has been built up.

Nicotinic acid, or pyridine β-carboxylic acid (sublimes at 228° to 229°), has been obtained by oxidation of various synthetic pyridine compounds, as well as of vegetable alkaloids (*e.g.* nicotine, pilocarpine, hydrastine, berberine). The constitution of this acid follows from its formation by the action of heat on quinolinic acid. Since the latter is obtained by the oxidation of quinoline (see later), it must contain its two carboxyl groups in the α- and β-positions. The acid produced from quinolinic acid by loss of one molecule of carbon dioxide must therefore be an α- or a β-acid. As the former structure has already been assigned to picolinic acid, it

[1] A. E. Tschitschibabin and co-workers, *Ber.*, 1924, **57**, 1168; 1927, **60**, 1607. For γ-amino-pyridine see E. Koenigs, *Ber.*, 1924, 1179. [2] Skraup and Cobenzl, *Monats.*, 4, 436.

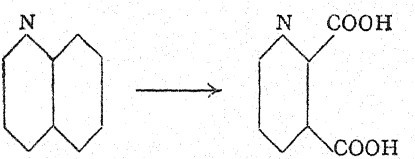
follows that nicotinic acid must be the β-compound. Nicotinic acid has recently been shown to be one of the components of the vitamin B group (see section on vitamins).

Isonicotinic acid, m.p. 309°, results from the oxidation of various γ-substituted derivatives of pyridine. In this case the carboxyl group must occupy the γ-position, since there are only three mono-carboxylic acids possible and the α- and β-compounds have been shown to be represented by picolinic and nicotinic acids respectively.

Coramine, $C_5H_4(CO.NEt_2)N$, the diethylamide of pyridine-β-carboxylic acid, resembles camphor in many of its physiological properties. In some respects its action is more powerful than that of camphor, *e.g.* on the blood pressure and respiration, in its stimulating action on the heart and as an antidote to morphine. Hence it is employed medicinally.[1]

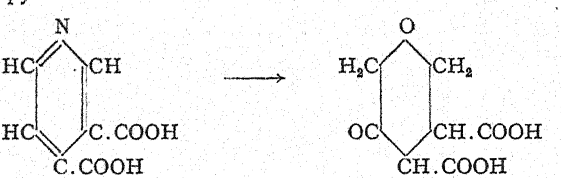
Each of the six possible *pyridine dicarboxylic acids*, $C_5H_3(COOH)_2N$, is known, and their constitutions have been established mainly by the researches of Hantzsch and his co-workers.

Quinolinic acid, *αβ-pyridine-dicarboxylic acid*, is formed by the oxidation of quinoline with alkaline permanganate, from which its constitution follows. It may be prepared in very good yield by oxidising 8-hydroxy-quinoline with concentrated nitric acid.[2]



Quinoline Quinolinic acid.

It melts at 192°, with evolution of carbon dioxide and conversion into nicotinic acid. **Cinchomeronic acid,** *βγ-pyridine-dicarboxylic acid*, is obtained as a degradation product of various cinchona alkaloids, such as quinine and cinchonine. It melts at 258° to 259°, with evolution of carbon dioxide to form a mixture of nicotinic and isonicotinic acids. Sodium amalgam converts it into the nitrogen-free *cinchonic acid*, a reaction which appears to be the reverse of that described on p. 670, by which derivatives of pyrone pass into those of pyridine.



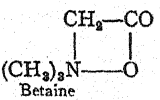
Cinchomeronic acid Cinchonic acid.

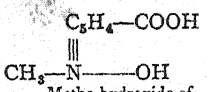
Lutidinic acid, *α γ-pyridine-dicarboxylic acid*, melting-point				235°.
Dinicotinic acid, *β β′-*	,,	,,	,,	323°.
Isocinchomeronic acid, *α β′-*	,,	,,	,,	236° to 237°.
Dipicolinic acid, *α α′-*	,,	,,	,,	226°.

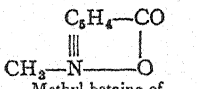
The higher acids of this series cannot be described here. It may, however, be mentioned that pyridine carboxylic acids give rise to an interesting type of compound, the

[1] Thannhauser and Fritzel, C., 1924, II, 2187. [2] E. Sucharda, *Ber.*, 1925, **58**, 1727.

constitution of which resembles that of betaine (see pp. 221 and 226); their methyl hydroxides are unstable and immediately part with water to form **betaines**:


Betaine


Metho-hydroxide of pyridine-carboxylic acid.

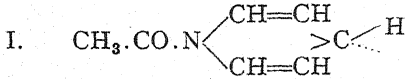

Methyl betaine of pyridine-carboxylic acid.

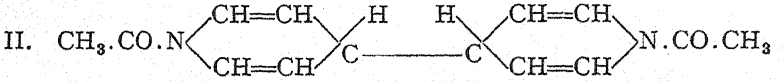
Hydro-pyridine Derivatives

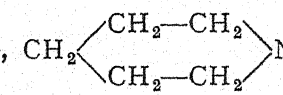
Derivatives of dihydro-pyridine are produced synthetically, as stated on p. 678, by the action of ammonia on diketo-compounds.

On reducing pyridine and its derivatives by means of sodium and alcohol, six atoms of hydrogen are taken up and hexahydro-compounds produced, 1 : 4-dihydropyridine being formed as an intermediate product.[1]

The reduction of pyridine with zinc dust and acetic anhydride leads to the formation of **NN'-diacetyl-(tetrahydro-$\gamma\gamma'$-dipyridyl)**) of formula II below. This is a crystalline compound, m.p. 124° to 125°, the production of which is explained by assuming that the reagents first attack the nitrogen atom with the temporary formation of the radical (I), which by union with itself yields the dipyridyl derivative (II).[2]





Piperidine, hexahydro-pyridine,  was first prepared from the alkaloid piperine, present in pepper, by heating with alkali. Its formation by synthetic methods, and by the reduction of pyridine (with sodium and alcohol or by electrolytic means), has already been mentioned in the foregoing pages.[3] It is a colourless liquid of peculiar ammoniacal smell, miscible in all proportions with water, alcohol, ether and benzene. It boils at 105°, solidifies at −17°, and is of sp. gr. 0·88 at 0°. Whereas pyridine is a weak tertiary base of aromatic character, piperidine is a strong secondary base, the entire behaviour of which classes it with the aliphatic amines. The imino-hydrogen atom of piperidine may be replaced by different radicals (alkyl, acyl, nitroso-groups, etc.), and numerous derivatives have thus been prepared which cannot be described here. On being heated at 300° with concentrated sulphuric acid, at 250° with nitrobenzene or at 180° with silver acetate, piperidine becomes oxidised to pyridine.

Alkaloids derived from piperidine are treated in a later chapter.

[1] B. D. Shaw, *J. C. S.*, 1925, 215. [2] O. Dimroth and co-workers, *Ber.*, 1921, 54, 2934; 1922, 55, 1223. [3] For the preparation of chemically pure piperidine compare Vorländer, *Ann.*, 1906, 345, 277.

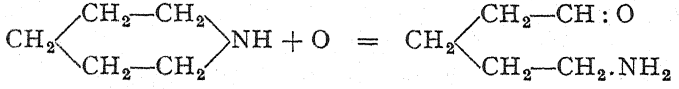
Tetrahydro-pyridine-3-aldehyde and *piperidine-3-aldehyde* have been prepared synthetically.[1]

As has been shown by J. v. Braun, alkylation of the carbon atoms strengthens the structure of the piperidine ring. This effect becomes apparent on the introduction of a single methyl group.[2]

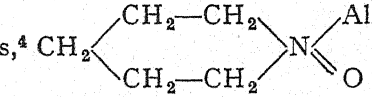
Methods of Opening the Piperidine Ring

A number of methods are available for rupturing the piperidine ring, processes which are in a sense a reversal of the syntheses described on pp. 677 *et seq.*

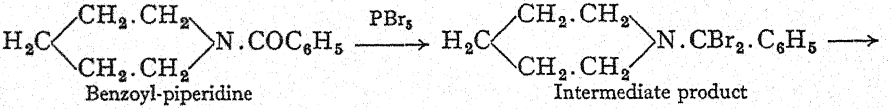
1. **By Oxidation.**—Under the influence of oxidising agents, such as hydrogen peroxide, the piperidine ring is comparatively easily broken between the nitrogen atom and an adjacent carbon atom, with the formation of δ-amino-valeraldehyde.[3]



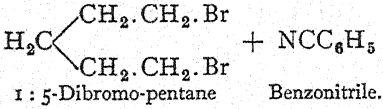
The opening of the ring is effected even more readily by the action of potassium permanganate on N-acylated piperidine derivatives. In this way benzoyl-piperidine, $C_5H_{10}N(COC_6H_5)$, yields benzoyl-δ-amino-valeric acid. On the other hand, when N-alkyl piperidines are treated with hydrogen peroxide they take up an oxygen atom to form alkyl-piperidine oxides,[4]



2. **By Means of Phosphorus Halides.**—The work of J. v. Braun [5] has shown that acyl derivatives of piperidine are very easily attacked by phosphorus pentachloride or pentabromide. Under chosen conditions the resulting 1 : 5-dichloro-pentane or 1 : 5-dibromo-pentane is obtained in so good a yield that the reaction can be used as a means of preparing these halogen compounds.[6]



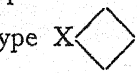
Benzoyl-piperidine — Intermediate product

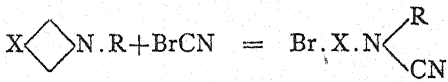


1 : 5-Dibromo-pentane — Benzonitrile.

3. **By Means of Cyanogen Bromide.**—J. v. Braun has also discovered

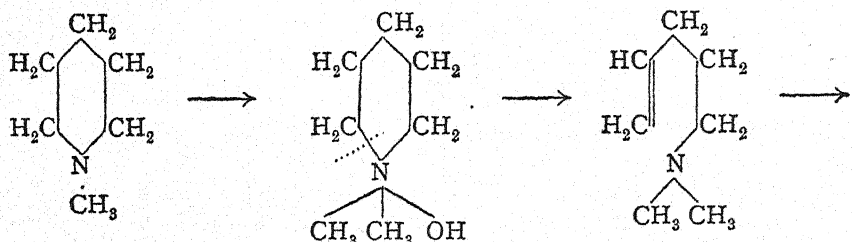
[1] A. Wohl and Losanitsch, *Ber.*, 1907, 40, 4685. [2] J. v. Braun and F. Zobel, *Ber.*, 1926, 59, 1786. [3] Wolffenstein, *Ber.*, 1892, 25, 2777. On reduction with zinc and hydrochloric acid δ-amino-valeraldehyde is converted back into piperidine. [4] Auerbach and Wolffenstein, *Ber.*, 1901, 34, 2411 ; 1911, 44, 1464. [5] *Ber.*, 1904, 37, 2915, 3210. [6] See also J. D. A. Johnson, *J. C. S.*, 1933, 1531. The above 1 : 5-dihalogen compounds are readily converted into the dicyano-derivatives, and by further hydrolysis into pimelic acid. This provides a convenient method of preparing *n*-pimelic acid. J. v. Braun, *Ber.*, 1904, 37, 3588.

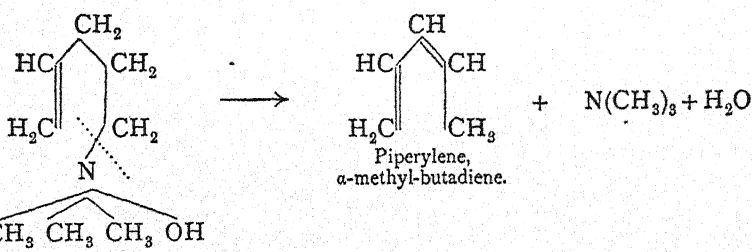
that substitution products of piperidine, and other cyclic tertiary bases of the general type  , are disrupted by cyanogen bromide[1] according to the following equation to give brominated cyanamides Br.XN(CN).R,



provided that the alkyl group R is not removed from the molecule. Such a cyanamide derivative may undergo hydrolysis to a brominated secondary amine, Br.X.NH.R. This constitutes the simplest available method of opening a ring containing nitrogen, and may also be employed with success in cases where (as with the aromatic derivatives of piperidine) the following method (4) cannot be applied.

4. **By Means of Exhaustive Methylation.**—A method of opening the piperidine ring, with simultaneous loss of nitrogen, is by "exhaustive methylation." This series of reactions, first used by A. W. Hofmann in the case of piperidine, was correctly interpreted by Ladenburg and later applied by other investigators to a large number of cyclic bases (see p. 617). It has been the classical weapon of attack in determining the constitution of the majority of vegetable alkaloids, and may therefore be treated in some detail. The operations are as follows: Piperidine, as a secondary base, can be methylated at the nitrogen atom by means





of methyl iodide. The methyl piperidine so obtained unites with methyl iodide to form dimethyl-piperidinium iodide, and this by treatment with moist silver oxide (or potassium hydroxide) is converted into dimethyl-piperidinium hydroxide. The latter on dry distillation breaks up into

[1] J. v. Braun, *Ber.*, 1907, 40, 3914; 1909, 42, 2219; 1911, 44, 1252.

water and a compound frequently described as dimethyl-piperidine, but correctly named Δ^4-pentenyl-dimethylamine. Being a tertiary base, this substance also unites with methyl iodide to form a substituted ammonium iodide, which when converted as before into the ammonium hydroxide and submitted to dry distillation yields trimethylamine, water and a hydrocarbon, α-methyl-butadiene, of the formula C_5H_8.

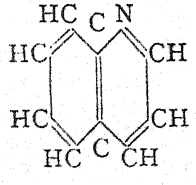
It has been mentioned on p. 618 that the addition product formed by Δ^4-pentenyl-dimethylamine with hydrochloric acid readily isomerises into the methochloride of 1 : 2-dimethyl-pyrrolidine, thus forming a connection between the pyridine and pyrrole series.

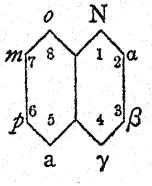
5. **By Reduction.**—When heated to 300° with hydriodic acid, piperidine decomposes into *n*-pentane and ammonia.

VI

Quinoline, Isoquinoline and Acridine Groups

Quinoline is related to pyridine in the same manner as naphthalene to benzene; and may be looked upon as αβ-benzo-pyridine, or a naphthalene in which one CH-group in the α-position is replaced by a nitrogen atom.





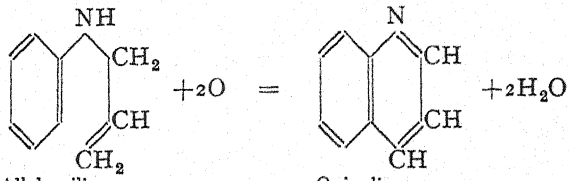
In this series the number of *isomeric substitution products* is very large. A glance at the formula for quinoline reveals the fact that no two hydrogen atoms are similarly situated with respect to the nitrogen atom. The position of substituents is best represented by making use of the above numbering as suggested by Richter. Substituents in the pyridine nucleus are also frequently indicated by means of the Greek letters α, β, γ, and in the benzene nucleus by the prefixes *o*-, *m*-, *p*-, and *ana*-.

Quinoline, C_9H_7N, is found in coal tar and bone oil, and is produced by distilling many alkaloids—particularly the cinchona alkaloids—with potassium hydroxide. It is a colourless, oily liquid which boils at 240°, solidifies at −19·5°, and is of sp. gr. 1·081 at 0°. It possesses a peculiarly characteristic smell, is almost insoluble in water and dissolves readily in alcohol, ether and the majority of organic solvents. In chemical properties it resembles pyridine, and like the latter is a tertiary base. With acids it unites to form salts, of which the bichromate, $(C_9H_7N)_2H_2Cr_2O_7$, is sparingly soluble.

Synthesis of Quinoline and its Derivatives

The formula given above is confirmed by a number of syntheses of quinoline, among which the following may be mentioned :

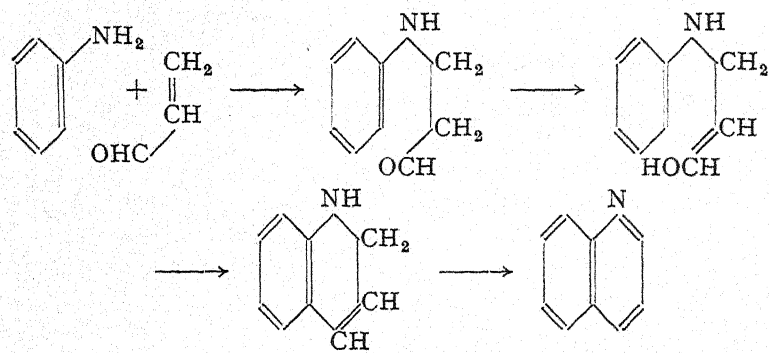
1. The first synthesis of quinoline was effected in 1879 by passing the vapour of allyl-aniline over lead oxide heated to redness (Königs).



Allyl-aniline Quinoline.

2. Preparations of quinoline and of those derivatives substituted in the benzene nucleus are based almost exclusively on *Skraup's synthesis.* This consists in heating an aromatic amino-compound with glycerol and sulphuric acid, in the presence of nitrobenzene or arsenic acid [1] as oxidising agent. Quinoline itself is obtained in this way by heating a mixture of aniline, glycerol and nitrobenzene with concentrated sulphuric acid.

The mechanism of the reaction is in all probability as follows : Under the dehydrating influence of sulphuric acid, glycerol is first converted into acrolein ; this condenses with aniline in the presence of the strong acid [2] to form β-phenylamino-propaldehyde, which loses water yielding a dihydroquinoline. The latter is then oxidised to quinoline by the nitrobenzene.



This reaction has proved extraordinarily fruitful, since the place of aniline may be taken by its homologues, halogen and nitro-substitution products, and also by amino-carboxylic acids, amino-sulphonic acids and amino phenols, thus enabling a great variety of quinoline derivatives to be prepared containing substituents in the benzene nucleus. In addition, aniline may be replaced by naphthyl-amines, with the formation of

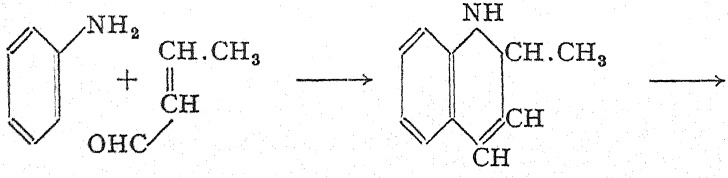
[1] Skraup, *Ber.*, 1881, 14, 1002. *Monats.*, 1880, 1, 3216 ; 1881, 2, 141. *Ber.*, 1896, 29, 703. The somewhat vigorous reaction may be modified and the yield increased by the addition of boric acid and ferrous sulphate, E. W. Cohn, *J. A. C. S.*, 1930, 3685. [2] Aniline may also unite with acrolein to give the anil (Schiff's base) $C_6H_5.NH : CH.CH : CH_2$, but this does not occur in the presence of a strongly hydrolysing agent such as sulphuric acid.

naphtho-quinolines ; and by making use of diamines two pyridine rings may be linked on to the benzene nucleus, the compounds so obtained being known as *phenanthrolines*.

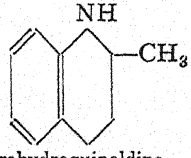
The preparation of alizarin blue described on p. 558, which was known before the discovery of Skraup's synthesis, is another example of this method of forming a quinoline derivative.

3. The *quinaldine syntheses* of Döbner and Miller [1] are also based on Skraup's synthesis. In these an aromatic amine, an aldehyde and concentrated hydrochloric acid are mixed together and heated. The reaction in the case of aniline and acetaldehyde (paraldehyde) is represented as follows. Acetaldehyde condenses to aldol, which is dehydrated to crotonaldehyde. The latter combines with aniline forming dihydroquinaldine (compare Skraup mechanism) and this then breaks down partly to quinaldine and partly to tetrahydroquinaldine. The Döbner-Miller synthesis

$$2CH_3.CHO \longrightarrow \underset{\text{Aldol.}}{CH_3.CHOH.CH_2.CHO} \longrightarrow \underset{\text{Crotonaldehyde.}}{CH_3.CH:CH.CHO}$$

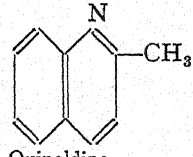


Dihydroquinaldine



Tetrahydroquinaldine

and

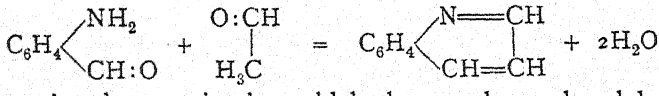


Quinaldine.

thus yields homologues of quinoline, and the Skraup method making use of glycerol appears to be a special case of the Döbner-Miller synthesis, modified by the addition of an oxidising agent. By employing other aldehydes of the formula $R.CH_2.CHO$ in place of acetaldehyde and other aromatic amines instead of aniline, it is possible to prepare in this manner a great number of quinoline derivatives.

γ-Methylquinoline or lepidine [2] is produced by the condensation of acetaldehyde with aniline in the presence of alumina at high temperatures.

4. Another synthesis of general application is that discovered by Friedländer,[3] who obtained quinoline by condensing *o*-amino-benzaldehyde with acetaldehyde.

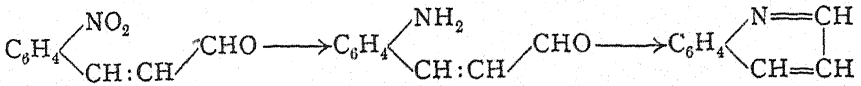


Once again, the *o*-amino-benzaldehyde may be replaced by its substitution products, by *o*-amino-phenyl ketones or *o*-amino-benzoic acid,

[1] *Ber.*, 1892, **25**, 2072, 2864; 1896, **29**, 59; 1903, **36**, 4013. W. Borsche, *Ber.*, 1908, **41**, 3884. [2] A. E. Tschitschibabin and M. P. Oparina, *Ber.*, 1927, **60**, 1873. [3] *Ber.*, 1882, **15**, 2572; **16**, 1833; 1892, **25**, 1752.

and in place of acetaldehyde other compounds containing the group $CH_2.CO$ may be used, *i.e.* aldehydes, ketones, acetoacetic ester and malonic ester. It has recently been shown [1] that these reactions proceed very readily in dilute aqueous solutions if the p_H value is carefully controlled.

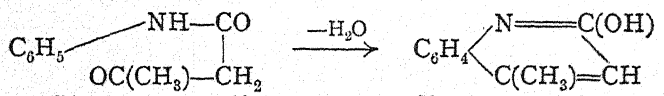
5. Baeyer and Drewsen prepared quinoline by the reduction of *o*-nitro-cinnamic aldehyde.



This reaction gives a clear insight into the constitution of quinoline and affords further proof that it is an ortho-derivative of benzene.

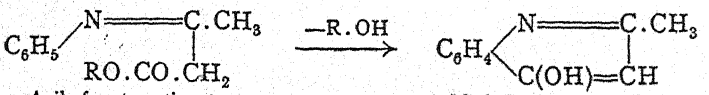
6. Hydroxy-derivatives of quinoline may be synthesised from the products formed by the condensation of β-ketonic acids with aromatic amines. By the interaction of acetoacetic ester and aniline, for example, two different products are obtained according as the reaction proceeds in the cold or at a moderate temperature. In the former case β-phenyl-amino-crotonic ester (anil of acetoacetic ester) is formed and in the latter the anilide of acetoacetic acid (Knorr).

It has been shown by Knorr [2] that the anilide of acetoacetic acid loses water on treatment with concentrated sulphuric acid and is converted into 2-hydroxy-4-methyl-quinoline (lepidone).



Anilide of acetoacetic acid — 2-Hydroxy-4-methyl-quinoline.

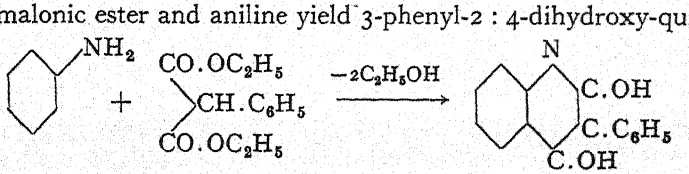
When the anil of acetoacetic ester is heated to 250° it yields 2-methyl-4-hydroxy-quinoline.



Anil of acetoacetic ester — 2-Methyl-4-hydroxy-quinoline.

This reaction can also be carried out by using benzoyl-acetic ester, acetone dicarboxylic ester, and other similar compounds in place of acetoacetic ester, and with homologues of aniline and also phenylene diamine as substitutes for aniline.

7. A simple synthesis of 2 : 4-dihydroxy-quinolines consists in heating alkylated and arylated malonic esters with aromatic amines.[3] Thus phenyl-malonic ester and aniline yield 3-phenyl-2 : 4-dihydroxy-quinoline.

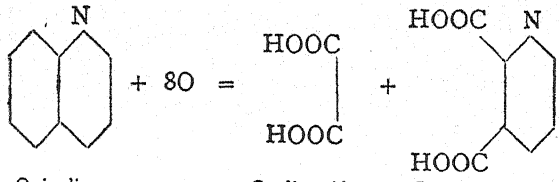


[1] C. Schöpf and G. Lehmann, *Ann.*, 1932, 497. [2] *Ann.*, **236**, 69, 112. [3] P. Baumgarten and W. Kärgel, *Ber.*, 1927, **60**, 832.

Properties of Quinoline

Quinoline and its homologues are liquids of characteristic odour, sparingly soluble in water, but dissolving readily in alcohol and ether. Being substituted derivatives of pyridine, they resemble the latter closely in chemical behaviour.

A point of considerable importance is the *behaviour of quinoline on oxidation*,[1] as this has provided valuable confirmation of the structure deduced from synthesis (see above). When quinoline is oxidised by means of alkaline potassium permanganate it yields quinolinic acid together with oxalic acid :



Quinoline Oxalic acid Quinolinic acid.

Whilst the syntheses already quoted indicate that quinoline is an ortho-disubstituted derivative of benzene, this degradation shows it to be a 2 : 3-disubstitution product of pyridine, thus completing the proof of the quinoline formula.

Similarly, in the homologues of quinoline the benzene nucleus is less stable to oxidation with permanganate than the pyridine nucleus, and pyridine carboxylic acids are again formed. On the other hand, oxidation with chromic acid in sulphuric acid solution attacks the side chain, leaving the quinoline nucleus intact and yielding quinoline carboxylic acids.

Quinoline, like pyridine, is not easily nitrated. The first products to be formed are 5- and 8-*nitro-quinolines*, which on further nitration yield 5 : 7- and 6 : 8-*dinitro-quinolines*.[2] The sulphonation of quinoline, in the same manner, leads only to substitution in the benzene nucleus. Sulphonic acids, in which the sulphonic group is attached to the pyridine ring, are obtained by oxidation of thio-quinolines with nitric acid ; or from quinolines containing chlorine in the pyridine nucleus, by double decomposition with alkali sulphite.[3] As with the chloro-pyridines (p. 680), only the chlorine atoms in the 2- and 4-positions in chloro-quinolines can be exchanged for basic radicals.

The 2- and 4-homologues of quinoline behave towards aldehydes in the same manner as those of pyridine (see pp. 680 *et seq.*).

As will be described in more detail under the hydroquinolines, hydrogen very readily adds on to the pyridine nucleus of quinoline.

Only a few of the large number of quinoline derivatives known can be treated here. Certain of these compounds are used in medicine or as dye-stuffs.

[1] For the degradation of quinoline by reduction see H. Emde, *Ann.*, 1912, **391**, 88. [2] Kaufmann and Hüssy, *Ber.*, 1908, **41**, 1785. [3] Besthorn and Geisselbrecht, *Ber.*, 1920, **53**, 1017.

Homologues of Quinoline

All of the seven theoretically possible methyl-quinolines are known. The four of these containing the methyl group in the benzene nucleus are generally termed *toluquinolines*.

Quinaldine, *2-methyl-quinoline*, $C_9H_6(CH_3)N$, is found with quinoline in coal tar, and can be prepared synthetically by the foregoing methods. It boils at 247°.

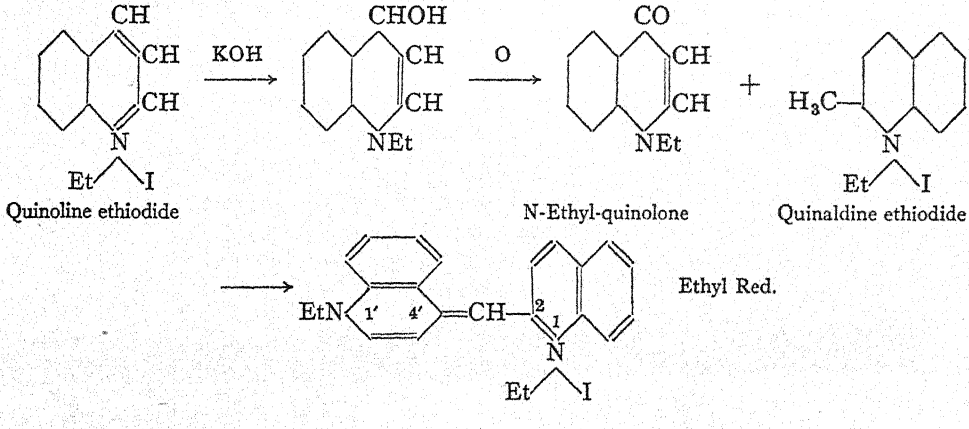
The sodium salt of quinaldine disulphonic acid is the dye-stuff **quinoline yellow.** This dyes a very pure and fast yellow, but owing to the high price its use is limited.

Lepidine, *4-methyl-quinoline*, b.p. 257°, is also present in coal tar and was isolated by Williams from the product obtained on distilling cinchonine with caustic potash. **6-Methoxy-lepidine,** m.p. 50° to 52°, was obtained from quinine by treatment with potassium hydroxide (Königs), and is formed synthetically by the condensation of *p*-anisidine with acetone and methylal.[1]

Flavaniline, *2-aminophenyl-4-methyl-quinoline*, may be produced by heating acetanilide with zinc chloride, or by the condensation of equimolecular proportions of *o*- and *p*-amino-acetophenones. Its monacid salts are beautiful yellow dyes, which dye wool and silk pure shades of yellow.

Cyanine Dyes

A valuable group of dye-stuffs known as **cyanines** is prepared from the alkiodides of quinaldine and lepidine. Although too fugitive for use in dyeing fabrics these are of the utmost importance for rendering photographic plates more sensitive to light of the redder end of the spectrum. The cyanines are strongly basic reddish-purple or blue compounds, which are built up of two quinoline nuclei joined in the 2- or 4-positions through a : CH. or : CH.CH : CH. group. Various structures are obviously possible according to the nature of this group and the points to which it is attached to the quinoline nuclei.

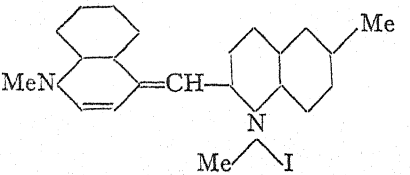


Quinoline ethiodide — N-Ethyl-quinolone — Quinaldine ethiodide

[1] A. Pictet and Misner, *Ber.*, 1912, 45, 1800.

Compounds containing the : CH. link are obtained by heating a quinoline alkiodide with an alkiodide of quinaldine or lepidine in the presence of caustic alkali. The reaction is one of aerial oxidation and proceeds through the intermediate formation of a quinolone. As may be seen from the foregoing examples, the methene group uniting the quinoline nuclei is derived from a methyl group attached to position 2 or 4 in one of the reacting molecules.

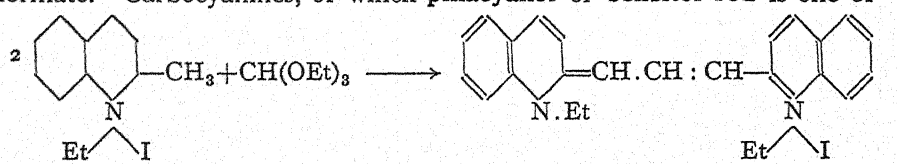
Products such as **ethyl red** (1 : 1′-diethyl-isocyanine), which contain a 2 : 4′-linking, are described as **isocyanines.**[1] The most important members of this group are ethyl red and **pinaverdol** or **sensitol green** (1 : 6 : 1′-trimethyl-isocyanine), the latter being prepared by heating a mixture of quinoline methiodide and *p*-toluquinaldine methiodide with alcoholic sodium hydroxide. These dyes sensitise photographic plates as far as the orange region.



Pinaverdol.

The isomeric compounds with a 4 : 4′-linking are known as **cyanines** and are of little value. They may be prepared by using a mixture of quinoline and lepidine methiodides with alkali. The corresponding 2 : 2′-derivatives (**μ-cyanines**) were first obtained by heating a mixture of 2-iodoquinaldine methiodide and quinaldine alkiodide with alcoholic potash.

Carbocyanines,[2] which contain the quinoline nuclei joined through a : CH.CH : CH. chain, were first isolated by adding formaldehyde to the reaction mixture employed for the preparation of *iso*cyanines. Miss Hamer has since shown [3] that the best yields are given when a quinaldine alkiodide is heated in pyridine solution with an excess of ethyl orthoformate. Carbocyanines, of which **pinacyanol** or **sensitol red** is one of



Quinaldine ethiodide

Pinacyanol.

the most important, sensitise photographic plates in the yellow and red regions.

Various other types of carbocyanines may also be prepared by Hamer's method. For example, **kryptocyanine,** (1 : 1′-diethyl-4 : 4′-carbocyanine iodide), is obtained by using lepidine ethiodide. This sensitises strongly in the red and infra-red, although not in the green.

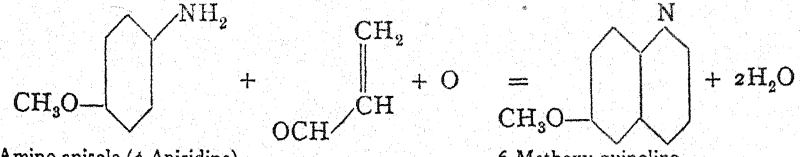
[1] See *The Synthetic Dye-stuffs* by Cain and Thorpe, revised by Thorpe and Linstead (Griffin, 1933). [2] The structure of the carbocyanines was first established by W. H. Mills and Miss Hamer, *J. C. S.*, 1920, 1550. [3] Hamer, *J. C. S.*, 1927, 2796. See also König, *Ber.*, 1922, 55, 3293.

Hydroxy-quinolines

The hydroxy derivatives of quinoline possess the basic character of quinoline as well as the acidic character of phenol.

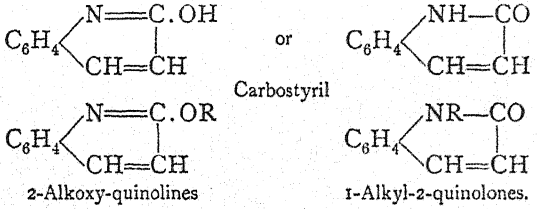
Among compounds containing the hydroxy group attached to the benzene nucleus, **loretine,** *7-iodo-8-hydroxy-quinoline-5-sulphonic acid*, $C_6HI(OH)(SO_3H) : C_3H_3N$, is used as a substitute for iodoform.

The *methyl ether of 6-hydroxy quinoline* has been known for a considerable time, and was first obtained by fusing the alkaloid quinine with caustic potash. It may be prepared synthetically by Skraup's method from *p*-amino-anisole, in the following manner :



p-Amino-anisole (*p*-Anisidine) 6-Methoxy-quinoline.

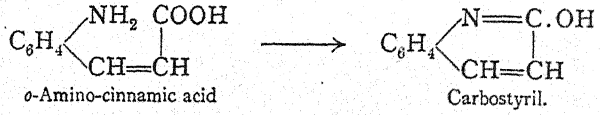
Hydroxy-quinolines containing the hydroxyl group in the 2- or 4-position of the pyridine nucleus exhibit the same peculiar tautomerism as the hydroxy-pyridines (see p. 681). They react in the hydroxylic form as true hydroxy quinolines, and also in the ketonic forms as quinolones. It has not yet been decided which structure represents the free compounds. On the other hand, the ethers exist in both modifications :



Carbostyril

2-Alkoxy-quinolines 1-Alkyl-2-quinolones.

Carbostyril, *2-hydroxy-quinoline*, is obtained synthetically by the methods described on p. 690, *e.g.* by the reduction of *o*-nitro-cinnamic acid, or by heating *o*-amino-cinnamic acid [1] (prepared from the *o*-chloro-acid). Hence it is to be regarded as an inner anhydride (lactam or lactim) of *o*-amino-cinnamic acid.



o-Amino-cinnamic acid Carbostyril.

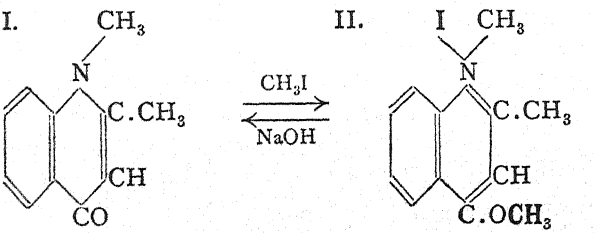
It can be prepared from quinoline by warming with a solution of bleaching powder. It crystallises with 1 mol. H_2O, and when anhydrous melts at 201°. With acids and alkalis it forms salts which are decomposed by water.

Kynurine, *4-hydroxy-quinoline*, is formed by heating kynurenic acid (see p. 632), or by the oxidation of cinchonine. It melts at 201°, and on treatment with phosphorus pentachloride yields 4-chloro-quinoline.

[1] H. Meyer and Beer, *Monats.*, 1913, 34, 1173.

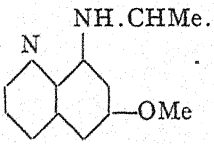
4-Quinaldone, *4-hydroxy-2-methyl-quinoline*, is obtained from the anil of acetoacetic ester (see p. 690), and gives two isomeric methyl ethers, *4-methoxy-quinaldine*, b.p. 298°, and *1-methyl-4-quinaldone* (I). It is worthy of emphasis that these two ethers yield one and the same methiodide with methyl iodide. The first compound adds the alkyl halide normally to the nitrogen atom ; the second, on the other hand, unites with methyl iodide by 1 : 5-addition, in the same manner as antipyrine (see pp. 658 *et seq.*), to form the methiodide of 4-methoxy-quinaldine (II). This methiodide shows a great resemblance to the *pseudo*-methiodide of antipyrine, and is easily converted into the original methyl-quinaldone by fusion or treatment with aqueous alkali.[1]

In this way it is therefore possible to convert 4-methoxy-quinaldine into 1-methyl-4-quinaldone. The rearrangement of bonds which occurs during the change is similar to that accompanying the isomerisation of the forms of a tautomeric substance.



Benzoyl chloride also combines with methyl quinaldone in the same manner as methyl iodide. The addition product is decomposed into its components instantaneously by aqueous alkali, and gradually by the action of cold water of boiling alcohol.

Plasmoquine, a derivative of 6-methoxy-quinoline, is employed as a specific against malaria.



Quinolyl Ketones

Quinoline-8-aldehyde, which strongly resembles benzaldehyde in properties, reacts with organo-magnesium halides to form *8-quinolyl-carbinols*. These, on oxidation with potassium bichromate and sulphuric acid, pass into the corresponding *8-quinolyl-ketones*.[2]

A productive method of preparing *4-quinolyl-ketones* lies in the action of organo-magnesium halides on esters and nitriles of quinoline-carboxylic acids,[3] *e.g.* 4-quinoline-carboxylic esters on treatment with ethyl magnesium iodide yield, among other products, *4-quinolyl-ethyl-ketone* :

$$NC_9H_6.COOR \longrightarrow NC_9H_6.CO.C_2H_5$$

[1] L. Knorr, *Ber.*, 1897, **30**, 922, 927. *Ann.*, 1903, **328**, 81. [2] Howitz and Köpke, *Ann.*, 1913, **396**, 38. [3] A. Kaufmann and co-workers, *Ber.*, 1913, **46**, 57. Rabe and Pasternack, *ibid.*, 1026.

The 4-quinolyl-ketones bear a distant structural resemblance to the *cinchona toxines*, which are degradation products of the chinchona alkaloids. They may be converted into amino-alcohols which are related to these alkaloids.

Quinoline Carboxylic Acids

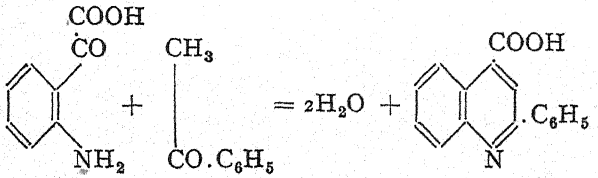
All of the carboxylic acids corresponding to the seven methyl quinolines are known. Those containing the carboxyl group in the benzene ring may be prepared from amino-benzoic acids by Skraup's synthesis.

Among quinoline carboxylic acids containing the carboxyl group in the pyridine ring, the following may be mentioned :

Quinaldinic acid, *quinoline-2-carboxylic acid*, results from the oxidation of quinaldine with chromic acid. The hydrated acid ($2H_2O$) melts at 156°. A convenient method of preparing quinaldinic acid in good yield consists in heating quinaldine with formaldehyde and oxidising the methylol-compound so obtained with nitric acid.[1]

Cinchoninic acid, *quinoline-4-carboxylic acid*, has been isolated from the products obtained on oxidising the alkaloid cinchonine with potassium permanganate, nitric acid or chromic acid, and is also formed by the oxidation of other cinchona alkaloids. It melts at 254°.

Atophane, *α-phenyl-quinoline-γ-carboxylic acid*, is used as a remedy in arthritic diseases owing to its power of removing uric acid from the system. It is obtained from isatic acid and acetophenone.



The examination of a large number of atophane derivatives [2] shows that the structure requisite for the above physiological action is a quinoline nucleus with an aryl group in position 2 and a carboxyl in position 3 or 4.

Quininic acid,[3] *6-methoxy-quinoline-4-carboxylic acid*, is a methoxy-derivative of cinchoninic acid. It was obtained by Skraup by oxidising the alkaloid quinine with chromic acid. The constitution of quininic acid is shown by its conversion into pyridine-2 : 3 : 4-tricarboxylic acid on oxidation with potassium permanganate, and by the formation of 6-hydroxy-quinoline when it is treated with hydrochloric acid and distilled. It is produced synthetically by condensing *p*-anisidine with methylal and pyroracemic ester, and hydrolysing the ester so formed.[4] It crystallises in prisms, which melt at 280° with decomposition.

[1] Königs, *Ber.*, 1899, **32**, 223. Besthorn and Ibele, *Ber.*, 1906, **39**, 2329. [2] J. v. Braun and L. Brauns, *Ber.*, 1927, **63**, 1253. [3] This compound is very often referred to as quinic acid. The name quininic acid, however, emphasises the relationship to cinchoninic acid and avoids confusion with tetrahydroxy-hexahydro-benzoic acid, which is found associated with quinine in nature and is also known as quinic acid (see p. 471). [4] A. Pictet and Misner, *Ber.*, 1912, **45**, 1800. Compare also A. Kaufmann, *Ber.*, 1922, **55**, 614.

Kynurenic acid, *4-hydroxy-quinoline-3-carboxylic acid,* occurs in the urine of dogs, in which as has been shown by Ellinger, it originates from tryptophane (p. 632). It does not appear to be formed in the human system. The constitution of the acid has been confirmed by synthesis.[1]

Hydroquinolines

Hydrogen readily adds on to quinoline and its derivatives. Treatment with zinc and hydrochloric acid, or sodium and alcohol, leads to four atoms of hydrogen being taken up by the pyridine nucleus with the formation of *tetrahydro-quinolines.* These possess the properties of secondary fatty aromatic amines.

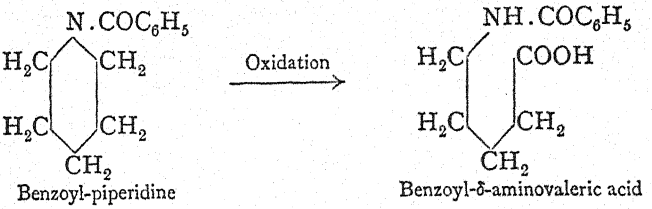
1 : 2-Dihydro-quinoline, $C_6H_4\begin{cases}NH.CH_2\\ \quad\quad |\\ CH:CH\end{cases}$, b.p. 226°, is obtained synthetically[2] by heating *o*-toluidine with chloro- or bromo-acetal in a sealed tube to temperatures above 200°. It is a colourless liquid which gradually turns yellow in air.

Tetrahydro-quinoline, $C_6H_4\begin{cases}NH—CH_2\\ \quad\quad |\\ CH_2—CH_2\end{cases}$, b.p. 245°, is a liquid at ordinary temperatures. Oxidising agents convert it into quinoline. In its general behaviour it shows a great resemblance to methylaniline. As indicated on p. 673, tetrahydro-quinoline may be transformed by various intermediate stages into *chromane.* This series of reactions represents the replacement of the imino-group of tetrahydro-quinoline by an oxygen atom.

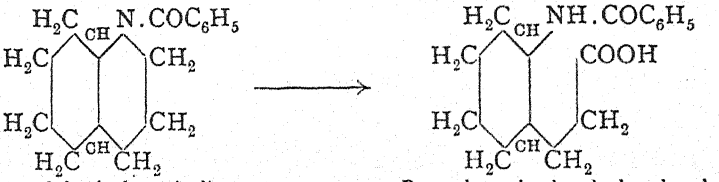
8-Hydroxy-1-methyl-tetrahydro-quinoline, $C_9H_9(OH)N.CH_3$, **kairine,** and *6-methoxy-tetrahydro-quinoline,* $C_9H_9(OCH_3)NH$, **thalline,** have been employed medicinally as febrifuges in the form of their salts.

Under the influence of very energetic reducing agents, such as hydriodic acid and phosphorus at high temperatures, quinoline or the tetrahydro-compound can be converted into **hexahydro-quinoline** (b.p. 226° under 720 mm.) and finally **decahydro-quinoline.**

$$\begin{array}{l}CH_2—CH_2—CH—NH—CH_2\\ \quad\quad\quad\



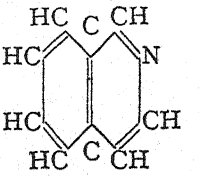
Benzoyl-piperidine — Benzoyl-δ-aminovaleric acid



Benzoyl-decahydro-quinoline — Benzoyl-*o*-amino-hexahydro-phenyl-propionic acid.

ISOQUINOLINE

Isoquinoline, like quinoline, represents the fusion of a pyridine ring with a benzene ring. In this case, however, the union is not in the $\alpha\beta$- but in the $\beta\gamma$-position of the pyridine nucleus, as will be seen from the following formula :

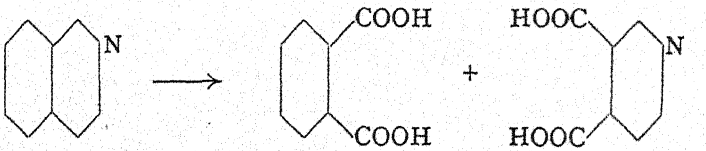


Isoquinoline.

Isoquinoline may therefore be considered as naphthalene in which one of the CH-groups in the β-position has been replaced by a nitrogen atom.

This constitution has been confirmed by the degradation of isoquinoline and its derivatives, as well as by synthesis.

By the **oxidation of isoquinoline** with potassium permanganate the benzene ring and the pyridine ring are both attacked, and a mixture of phthalic acid and cinchomeronic acid is obtained.

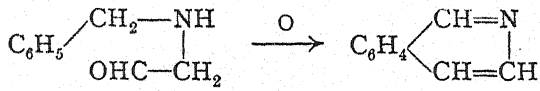


Isoquinoline. — Phthalic acid — Cinchomeronic acid.

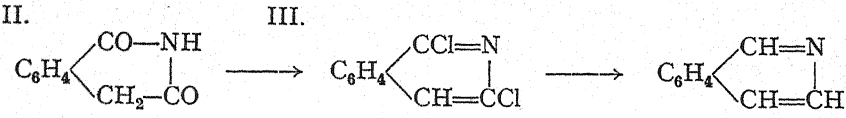
Among **syntheses** proving the structure of isoquinoline and its derivatives, the following may be mentioned :

1. Benzylamino-acetaldehyde (I), and also benzylidene-amino-acetal,

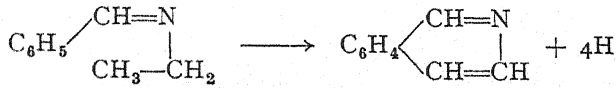
$C_6H_5CH:N.CH_2.CH(OC_2H_5)_2$, readily pass into isoquinoline under the influence of fuming sulphuric acid.

I. 

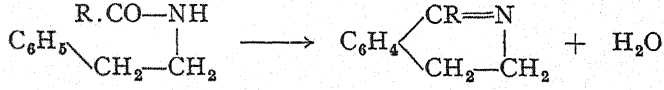
2. A useful synthetic method of preparing isoquinoline, which starts from homophthalic acid, is due to Gabriel (1886). Ammonium homophthalate on distillation yields *homophthalimide* (II); this when heated with phosphorus oxychloride is converted into *dichloro-isoquinoline* (III), from which by reduction with hydriodic acid and phosphorus is obtained isoquinoline.

II. III. 

3. Isoquinoline may also be produced by passing the vapour of benzylidene-ethyl-amine through a tube heated to redness [1]:

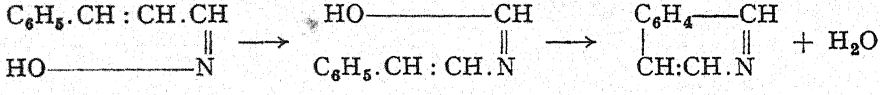


4. Acyl derivatives of ω-phenyl-ethylamine can be condensed to derivatives of dihydro-isoquinoline, *e.g.* by use of phosphorus pentachloride or oxychloride.[2]



Of the numerous syntheses effected in this way one of the most important is that of hydrastinine (see later). This synthesis also throws some light on the origin of isoquinoline complexes in plants.

5. An interesting synthesis of isoquinoline is by anhydride formation from cinnamic aldoxime, on warming with P_2O_5. This reaction is probably analogous to the Beckmann transformation, the phenyl-vinyl group ($C_6H_5.CH:CH$) and the hydroxyl radical first changing places, and water subsequently being liberated [3]:



Isoquinoline is found in small amounts with quinoline in coal tar, and can be separated from the latter by taking advantage of the low solubility of its sulphate. It is a colourless liquid, m.p. 23° and b.p. 240°, which in smell and other properties strongly resembles quinoline.

It is of importance on account of the fact that certain well-known vegetable alkaloids, such as papaverine, laudanosine, narcotine and

[1] Pictet and Popovici, *Ber.*, 1892, **25**, 733. [2] A. Pictet and Kay, *Ber.*, 1909, **42**, 1973. Pictet and Spengler, *Ber.*, 1911, **44**, 2030. H. Decker and co-workers, *Ann.*, 1913, **395**, 299.
[3] Bamberger and Goldschmidt, *Ber.*, 1894, **27**, 1954, 2795.

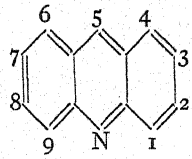
hydrastine, are derived from it. In the description of these substances given later a number of isoquinoline derivatives obtained from them by degradation will also be met with.

Acridine Group

Acridine is a dibenzo-pyridine, and stands to quinoline in the same relationship as anthracene to naphthalene. It may be regarded as anthracene in which one of the central CH-groups is replaced by N.[1]

The numbering of the nucleus now generally adopted in British and American publications is given in I; that shown in II is usually found in German journals. The former numbering is used in this text.

Acridine occurs in the crude anthracene of coal tar, and is the parent substance of various dye-stuffs of industrial value. It crystallises in

I. 

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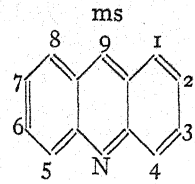


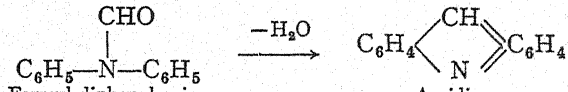
II.

colourless needles, which sublime easily and melt at 110°. In solution it has a blue fluorescence, a property peculiar to all the acridine bases. This fluorescence is particularly pronounced in ethereal solution.

The acridines are weaker bases than the pyridines or quinolines, and are marked by their great stability.

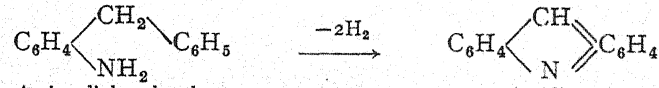
They are formed synthetically by various methods, *e.g.*:

1. By the action of zinc chloride on acyl derivatives of diphenylamine. Thus formyl-diphenylamine (from diphenylamine and formic acid) yields acridine when heated with zinc chloride.

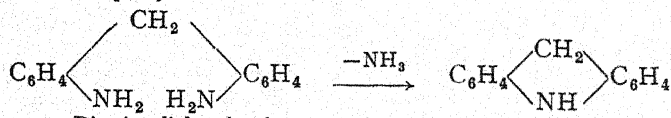


Formyl-diphenylamine — Acridine.

2. *o*-Amino-diphenylmethane is converted into acridine on oxidation [2]: and ammonia can be eliminated from *o*-diamino-diphenylmethane and



o-Amino-diphenylmethane — Acridine.



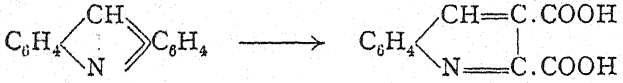
o-Diamino-diphenylmethane — Hydro-acridine.

[1] For constitution see K. v. Auwers and R. Kraul, *Ber.*, 1925, **58**, 543. [2] O. Fischer and Schütte, *Ber.*, 1893, **26**, 3085. For *syntheses of naphthacridines, cf.* F. Ullmann and co-workers, *Ber.*, 1900, **33**, 905; 1903, **36**, 1027; **37**, 2922; **39**, 298, 356. For the formation of *derivatives* of N-*phenyl-acridine* see F. Mayer and Freund, *Ber.*, 1922, **55**, 2049.

o-diamino-triphenylmethane with the formation of *hydro-acridines*. Tetra-amino-diphenyl-methane yields 2 : 8-*diamino-acridine*.[1] *o*-Nitro-diphenylmethane at high temperature (300°) passes into 5-*acridone*.[2]

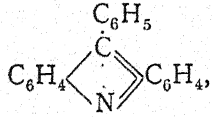
Tetrahydro-acridines result from the condensation of aromatic *o*-amino-aldehydes (or *o*-amino-ketones) with hydroaromatic ketones [3] containing the group CH_2CO.

The constitution of acridine follows from these syntheses, and is further confirmed by the formation of quinoline-2 : 3-dicarboxylic acid, known as *acridinic acid*, when acridine is oxidised with potassium permanganate :



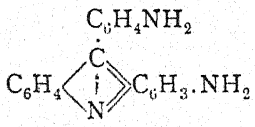
By the entrance of amino-groups (auxochromes) into the acridine molecule it acquires the properties of a dye, the pyridine ring functioning as the chromophore group. The resulting dye-stuffs generally contain the amino-groups in positions 2 and 8.

Acridine yellow, 3 : 7-*dimethyl*-2 : 8-*diamino-acridine*, is prepared by condensing *m*-tolylene-diamine with formaldehyde, whereby tetramino-ditolylmethane is first produced. On being heated with hydrochloric acid this loses ammonia and forms 3 : 7-dimethyl-2 : 8-diamino-hydro-acridine, which on oxidation yields the dye-stuff. Acridine yellow gives beautiful fluorescent colourings, particularly on silk, but these are not very fast to light.

From *phenylacridine*,  , are derived the benzo-flavines and chrysanilines.

Benzoflavine, 2 : 8-*diamino-phenylacridine*, is obtained in a similar manner to acridine yellow by the condensation of benzaldehyde (in place of formaldehyde) with *m*-phenylene diamine. The commercial product appears to be prepared from *m*-tolylene diamine and, with the aid of tannin, dyes cotton, wool and silk a fine yellow colour.

Chrysaniline, 5-*p-aminophenyl*-3-*amino-acridine*,



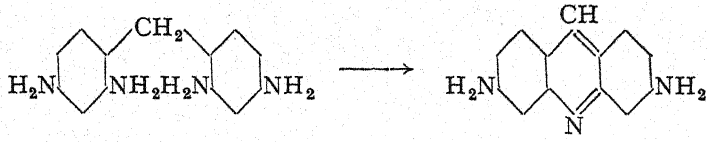
is formed as a by-product in the preparation of fuchsine. Its constitution has been established by O. Fischer and Körner, by synthetic and analytical methods. For example, on diazotisation and boiling with alcohol it gives *ms*-phenylacridine. It may be synthesised by the condensation of

[1] L. Benda, *Ber.*, 1912, 45, 1787. [2] A. Kliegl, *Ber.*, 1909, 42, 591. [3] Borsche and co-workers, *Ber.*, 1908, 41, 2203.

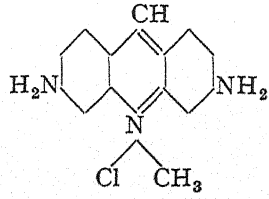
o-nitrobenzaldehyde with aniline to form *o*-nitro-*p*-diamino-triphenylmethane; the latter can then be reduced to the triamino-compound, which yields chrysaniline on oxidation. The crude nitrate or hydrochloride is placed on the market under the name of **"Phosphine."** It dyes wool and silk directly and cotton with the aid of tannin mordant, giving an orange-tinted yellow colour. It is chiefly used for silk.

Among acridine derivatives which are utilised as antiseptics the following may be mentioned.

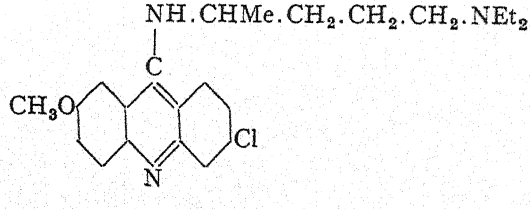
Proflavine, trypaflavine, 2 : 8-diamino-acridine sulphate, is prepared by dinitration of 4 : 4′-diaminodiphenylmethane followed by reduction to the 2 : 4 : 2′ : 4′-tetramino compound. On heating the latter in an autoclave ring closure is effected with loss of ammonia and production of proflavine. It forms reddish brown crystals and is used for wounds and in cases of gonorrhœa.



The methochloride of 2 : 8-diamino-acridine is a valuable antiseptic, the hydrochloride of which is employed under the name of **acriflavine.** It forms yellow crystals.



5 : 8-Diamino-acridine and its substitution products are also therapeutically effective against streptococci. The highest activity in this sense is shown by **rivanol,** the hydrochloride of 3-ethoxy-5 : 8-diamino-acridine. **Atebrin,** which is employed in the treatment of malaria, has been formulated as follows :



VII

The Vegetable Alkaloids[1]

Introduction

The alkaloids are now generally defined as basic compounds of vegetable origin, in which at least one nitrogen atom forms part of a cyclic system. This definition, however, does not include certain members of the group. Many of these compounds possess curative properties and are of great value in medicine.

Although the poisonous and therapeutic properties of various plants have been known and utilised from early times, it was not until 1817 that the first alkaloid was isolated.. A large number of these compounds are now known, but for a long time all attempts to determine their constitutions or to prepare them synthetically were fruitless.

The chemistry of the alkaloids began to make definite progress with the discovery of pyridine and quinoline, which led to the view that they were related to these bases in the same manner as aromatic compounds to benzene. Königs, in 1880, defined alkaloids as naturally occurring organic bases which are derived from pyridine.

This suggestion proved of great value in promoting our knowledge of the chemistry of pyridine, but did not hold true for all alkaloids. Later, the systematic classification of the alkaloids as derivatives of pyridine, or indeed as belonging to any single class of organic compound, had to be abandoned, owing to the discovery that natural groups of vegetable bases, such as the morphine and coca groups, cannot be referred to any one parent substance but belong to a number of different systems.

In describing all the vegetable bases as alkaloids, we are therefore collecting into one class a number of substances of widely differing constitutions. A few of these contain nitrogen in an open chain, but in general it is present in a cyclic structure such as that of pyridine, quinoline, isoquinoline or pyrrole. Still other alkaloids are derived from purine, or from complex dicyclic systems such as are contained in the "second half" of the cinchona alkaloids and in the tropine group.

Preparation of Alkaloids from Plants and their general Properties.[2]

Alkaloids are usually found in plants in the form of salts—in which they are either united to the common plant acids (*e.g.* malic or citric acid) or to certain characteristic acids such as quinic acid, in the cinchona

[1] See T. A. Henry, *The Plant Alkaloids* (Churchill, 1924). J. Schmidt, *Über die Erforschung der Konstitution und die Versuche zur Synthese wichtiger Pflanzenalkaloide* (Enke, 1900). *Handbuch der biologischen Arbeitsmethoden*, edited by E. Abderhalden (Berlin, 1920). J. Schwyzer, *Die Fabrikation der Alkaloide* (Springer, 1927). E. Späth, "Neuere Ergebnisse der Alkaloid-chemie," *Zeitschr. f. ang. Ch.*, 1928, 41, 1234, 1257. [2] See also Henry, *loc. cit.*

alkaloids, and meconic acid, in those of the opium group. Their distribution is very unequal. Although they may be detected in all parts of the plant, they generally accumulate in the fruit and seeds, and also in the bark of trees.[1]

In the preparation of alkaloids from plants the finely divided material is usually extracted with water containing hydrochloric or sulphuric acid. This liberates the alkaloids from their salts with organic acids, and the bases pass into solution as hydrochlorides or sulphates, together with dye-stuffs, carbohydrates and other products from the plant tissue. From the solution so obtained the alkaloids, being insoluble or only sparingly soluble in water, can be precipitated by the addition of alkali. If the bases are volatile, as in the case of nicotine, the solution or finely divided raw material is treated with alkali and distilled in steam. The crude alkaloids are then purified by special methods, frequently by recrystallisation of the free compounds or their salts.

The majority of the alkaloids are solid substances which cannot be distilled; only a few, such as coniine, are liquid and volatilise without decomposition. On the animal organism, as has already been mentioned, they often exert a marked physiological action. Almost without exception they are either insoluble or sparingly soluble in water, dissolve with more or less difficulty in chloroform, ether and benzene, and readily in alcohol. Most of the alkaloids are optically active and usually laevorotatory. In many cases their solutions give a strong alkaline reaction.

All of them form salts with acids, among which the hydrochlorides, sulphates and oxalates crystallise particularly well. Like the salts of other bases, they possess the property of uniting with certain metallic salts such as the chlorides of mercury, platinum and gold, to form double compounds.

Alkaloids are precipitated from aqueous or acid solution by a number of substances generally known as *alkaloid reagents*, *e.g.* tannic acid, picric acid, picrolonic acid, perchloric acid, potassium mercuric iodide, potassium bismuth iodide, phosphomolybdic acid and phosphotungstic acid. These reagents, however, are of no great value for the quantitative analysis of alkaloids, since the resulting compounds are not sufficiently insoluble and because the reagents also precipitate other organic substances.

Methods of Determining the Chemical Constitution of Alkaloids

In attempting to determine the structure of an alkaloid one of the first tasks is to investigate the action of *hydrolysing agents*. When heated with water, acids or alkalis, many of the vegetable bases break up into a characteristic alkaloidal constituent, containing nitrogen, and a nitrogen-free component. In general, the latter consists of an acid, the carboxyl group of which was originally combined with the basic group or with an

[1] On the mode of formation of alkaloids in plants see Pictet, *Ber.*, 1907, 40, 3771. Robinson, "A Theory of the Mechanism of the Phytochemical Synthesis of Certain Alkaloids," *J. C. S.*, 1917, 111, 876; R. C. Menzies and R. Robinson, *J. C. S.*, 1924, 2163.

alcoholic hydroxyl of the nitrogenous constituent; in the comparatively rare gluco-alkaloids, among which is numbered solanine, the second component is a sugar.

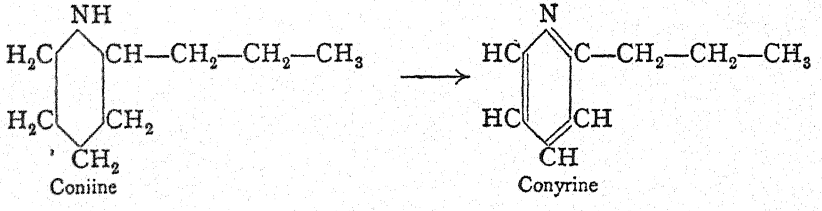
Thus piperine decomposes on hydrolysis into piperidine and piperic acid; the union in this case is of the acid amide type.

$$(C_5H_{10})N\begin{matrix}H\\ \vdots\end{matrix}\!\!-\!\!\begin{matrix}\vdots\\ OH\end{matrix}\!\!-CO-C_{11}H_9O_2$$

Atropine, as will be seen later, may be hydrolysed to give tropic acid and the alkamine tropine.

A second method is to effect a *degradation by distillation with zinc dust, fusion with alkali*, or *heating with bromine* or other vigorous reagents, as a result of which some stable parent substance can often be isolated.

Gerhardt, as early as 1842, obtained quinoline from cinchonine by distilling the latter with alkali. Vongerichten and Schrötter isolated phenanthrene as the main product of the distillation of morphine with zinc dust. Alkaloids containing oxygen generally lose this element on treatment with zinc dust, while those rich in hydrogen become dehydrogenised. Our knowledge of the constitution of coniine, for example, is based on Hofmann's observation that on distilling the compound with zinc dust it loses six hydrogen atoms to give conyrine (2-propyl-pyridine).



Coniine Conyrine

Other methods of removing hydrogen have already been quoted under piperidine (see p. 684). Meroquinene has been shown to be a pyridine derivative by Königs, who obtained 3-ethyl-4-methyl-pyridine by heating it with hydrochloric acid and mercuric chloride.

In the *hydrogenation of alkaloids* an important part is played by *catalytic methods of reduction*, involving the use of metals of the platinum group. In this manner morphine readily yields dihydro-morphine, and the cinchona alkaloids give dihydro-derivatives.

In addition, the *estimation of the methylimino-group*, as developed by Herzig and Meyer,[1] is employed in alkaloid investigation. When the hydriodides of N-methylated bases are heated at 200° to 300°, they part with methyl iodide according to the equation

$$R:N\begin{matrix}CH_3\\ H\\ I\end{matrix} = R:NH + CH_3I$$

[1] J. Herzig and H. Meyer, *Monats.*, 15, 613; 16, 599; 1897, 18, 379. *Cf.* also M. Busch, *Ber.*, 1902, 35, 1565. H. Decker, *Ber.*, 1903, 36, 2895.

The methyl iodide can be estimated by Zeisel's method, in which it is absorbed in an alcoholic silver nitrate solution and the resulting silver iodide weighed.

Zeisel's method for the determination of methoxyl groups depends on the conversion of the methyl of the CH_3O-group into methyl iodide, by treatment with hydriodic acid at the boiling-point, and the subsequent estimation of iodine in the above manner.

A process for the *determination of methoxyl in the presence of methylimino groups* (Herzig and Meyer) is based on the fact that the methoxyl group is hydrolysed at the boiling-point of hydriodic acid, whilst the N-methyl group is not detached until a higher temperature has been reached. With regard to the value of this method for distinguishing between a methoxyl and a methylimino group, it appears that a negative result at the lower temperature may safely be taken to prove the absence of methoxyl, but otherwise no certain conclusion can be drawn without further information.[1]

Fourthly, *the function of the oxygen atoms* in the alkaloid must be investigated. In this connection a reaction of special importance is the conversion of an alkaloid containing an alcoholic hydroxyl group into its anhydro-compound, by means of dehydrating agents such as a solution of glacial acetic acid in sulphuric acid (*e.g.* tropine —→ tropidine):

$$(C_6H_{11}N)\begin{matrix}-CHOH\\ |\\ -CH_2\end{matrix} = (C_6H_{11}N)\begin{matrix}-CH\\ \|\\ -CH\end{matrix} + H_2O$$

Tropine — Tropidine.

or by successive treatment with phosphorus chlorides and alcoholic potash (*e.g.* production of cinchene and quinene from cinchonine and quinine). The unsaturated compounds so obtained are often more reactive than the original alkaloids, and can with advantage be submitted to reactions involving further degradation.

Alcoholic and phenolic hydroxyl groups are estimated in the usual manner by acetylation and benzoylation.

Finally, the determination of the structure of an alkaloid generally necessitates an *investigation of the oxidation products*. Towards oxidising agents alkaloids offer a number of points of attack, such as ethylene linkings, $>C=C<$, carbinol groups, $\rangle C\langle^{H}_{OH}$, methyl-imino groups, $>N.CH_3$, and others.

Among the reagents used for this purpose the most important are potassium permanganate, chromic acid, nitric acid, and hydrogen peroxide. Permanganate is of particular value in attacking a double bond between carbon atoms, when two hydroxyl groups are first added (see p. 121). The resulting glycols are best further oxidised by means of chromic acid,

[1] See M. Busch, *Ber.*, 1902, **35**, 1565; G. Goldschmiedt, *Monats.*, 1906, **27**, 849; 1907, **28**, 1163; A. Kirpal, *Ber.*, 1908, **41**, 819.

which leads to the molecule being ruptured at the point originally occupied by the double bond.

Hydrogen peroxide brings about oxidation at the nitrogen atom and opens up the ring. In the case of saturated compounds of an aliphatic nature, permanganate has the peculiar property—often observed in the tropine series—of oxidising the methyl group away from nitrogen.

A good example of the use of oxidation methods will be described later in connection with nicotine.

An interesting method frequently employed in examining the structure of alkaloids is to study the degradation products they yield on *exhaustive methylation*, by which in its widest sense is understood the decomposition of substituted ammonium hydroxides under the influence of heat, or of quaternary ammonium salts when treated with alkalis. The reactions employed in the exhaustive methylation of alkaloids are well illustrated by the degradation of N-methyl-piperidine to piperylene (see p. 686), a classical example discovered by A. W. Hofmann. Another simple example will be found under aporphine, p. 762. In this manner the carbon framework of the alkaloid molecule is revealed in the form of unsaturated hydrocarbons.

This method of decomposition may be applied to alkaloids with all conceivable groupings in the molecule, and also, which is of special importance, to amino-acids obtained by the oxidation of alkaloids. The degradation products formed in this way include a great variety of unsaturated non-nitrogenous compounds, including hydrocarbons, ketones, aldehydes and carboxylic acids. For determining the structure of alkaloids this method is therefore of great service, since these unsaturated products of exhaustive methylation can often be converted by simple reactions, such as reduction, into compounds of known constitution.

Tropinic acid, for example, on exhaustive methylation gave a diolefin-dicarboxylic acid of the formula $C_7H_8O_4$, and of unknown structure ; on reduction with sodium amalgam this was transformed into pimelic acid, a normal dicarboxylic acid containing seven carbon atoms (see p. 276).

Hence it follows that the carbon skeleton in tropine and ecgonine must possess an unbranched chain of seven atoms, and that these are arranged in the form of a ring, since tropinic acid is produced from tropine and ecgonine by rupture of part of the cyclic system. The application of the same principle also enabled this cycloheptane ring to be isolated intact from cocaine and atropine, in the form of its ketone, suberone.

The value of exhaustive methylation, followed by reduction of the resulting degradation products, is not confined to the information this gives concerning structure, as it is often possible to effect a synthesis of the alkaloid by applying the method in the reverse direction.

The *fission of cyclic bases by means of phosphorus halides* (J. v. Braun) has also been applied to the determination of alkaloid structure. This treatment yields open-chain halogen compounds (see p. 685).

Information as to the effect of high temperature on an alkaloid can sometimes be gained by *fusion with urea*. The behaviour of berberine, narcotine and hydrastine has been examined under these conditions.[1]

Classification of the Alkaloids.—In the succeeding pages the alkaloids are classified according to their chemical constitution, especially with reference to the basic compounds from which they are derived. In most cases it is then found that alkaloids produced by one and the same plant, and therefore belonging to the same botanical group, also fall into the same chemical group, owing to the fact that the compounds generated by a given plant frequently possess similar chemical constitutions.

The alkaloids are therefore divided into the following groups :

1. Hydroxy-phenyl alkylamine and phenyl hydroxy-alkylamine bases.
2. Alkaloids of the pyridine group.
3. Alkaloids of the pyrrolidine group.
4. Alkaloids of the quinoline group.
5. Alkaloids of the isoquinoline group.
6. Alkaloids of the phenanthrene group.
7. Alkaloids of the purine group. (These have already been treated on pp. 341 *et seq.*)

Like every classification this is somewhat arbitrary. It may be objected that the alkaloids atropine and cocaine, treated under the pyrrolidine group, also contain a pyridine nucleus, and should therefore have been included in the pyridine group. It seemed, however, more convenient to treat these compounds in a group by themselves. The sixth group is termed the phenanthrene group, and under this head will be found morphine, codeine and thebaine. Each of these contains a phenanthrene nucleus, but the basic complex from which they are derived has not yet been determined with certainty.

I.—HYDROXY-PHENYL ALKYLAMINE AND PHENYL HYDROXY-ALKYLAMINE BASES

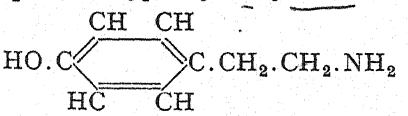
For **galegine**, $(CH_3)_2C : CH.CH_2.N : C(NH_2)_2$, the alkaloid of *Galega officinalis*, see E. Späth and W. Spitzy, *Ber.*, 1925, **58**, 2273.

In recent years organic bases possessing phenolic character have attracted ever-increasing attention, on account of their pharmacological properties. Adrenaline (see p. 843) has become an important drug ; the valuable properties of hordenine, present in fermenting barley, have been pointed out by Léger ; and Barger has identified in *p*-hydroxy-phenyl-ethylamine one of the constituents of ergot (in diseased rye seed) which gives rise to its characteristic activity. In addition to these compounds, thyroxine, which is described in the section on hormones, has been synthesised by Barger and Harington.

This compound has been shown by Barger [2] to be present to the

[1] Frerichs, *Arch. d. Pharm.*, 1903, **241**, 259. [2] G. Barger, *J. C. S.*, 1909, **95**, 1123. An even more active principle, *ergometrine*, has since been isolated from ergot by H. W. Dudley (*Proc. Roy. Soc.*, 1935, B, **118**, 478).

p-Hydroxyphenyl-ethylamine



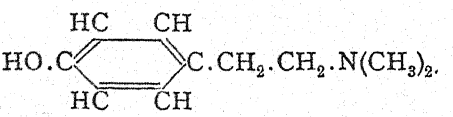
extent of 0·1 to 1 per cent. in ergot, in which it is accompanied by 4-β-aminoethyl-glyoxaline (β-iminazyl-ethylamine). Physiologically, it has the effect of strongly increasing the blood pressure. It may be isolated from the aqueous extract of ergot by shaking out with amyl alcohol, and crystallises in white needles or leaflets, m.p. 160°, b.p. 161° to 163°/2 mm. pressure. *p*-Hydroxyphenyl-ethylamine may be synthesised by various methods, *e.g.* benzyl cyanide on reduction yields phenyl-ethylamine, the benzoyl derivative of which is converted into the hydroxy-phenyl compound by nitration, followed by reduction and diazotisation. On removing the protective benzoyl group by hydrolysis, *p*-hydroxyphenyl-ethylamine is obtained.[1]

$$C_6H_5.(CH_2)_2NH.COC_6H_5 \longrightarrow NO_2.C_6H_4(CH_2)_2.NH.COC_6H_5 \longrightarrow NH_2.C_6H_4(CH_2)_2.NH.COC_6H_5 \longrightarrow HO.C_6H_4(CH_2)_2NH.COC_6H_5 \longrightarrow HO.C_6H_4(CH_2)_2.NH_2$$

A better yield is obtained by condensing anisaldehyde with nitromethane to form *p*-methoxy-nitrostyrole, which is then reduced and the methyl group removed with hydriodic acid.[2]

$$CH_3O.C_6H_4.CHO + H_3C.NO_2 \longrightarrow CH_3O.C_6H_4.CH{:}CH.NO_2 \longrightarrow CH_3O.C_6H_4.CH_2.CH_2.NH_2 \longrightarrow HO.C_6H_4\ CH_2.CH_2.NH_2$$

Hordenine, *p*-Hydroxyphenyl-dimethylethylamine



Hordenine is present in the embryo of barley. The researches which led to its discovery were prompted by the use made of germinating barley in southern France and some of the French colonies as a remedy for diarrhœa, dysentery and cholera, and the fact established later that cholera germs do not develop in an aqueous extract of germinating barley. Hordenine is prepared by extracting air-dried malt with alcohol; it boils at 173° to 174° (11 mm. pressure), and forms crystals of melting-point 117·5°, which are soluble in water, alcohol and ether. Hordenine sulphate raises the blood pressure and increases the flow of urine. It is a remedy for diarrhœa and dysentery, and in general gives good results in cases where barley can be used with success.

On methylation by means of dimethyl sulphate, followed by oxidation with potassium permanganate in alkaline solution, hordenine is converted

[1] Barger and Walpole, *J. C. S.*, 1909, **95**, 1720. [2] K. W. Rosenmund *Ber.*, 1909, **42**, 4778. For the preparation of other bases of this type see *Ber.*, 1910, **43**, 189.

into anisic acid. When degraded by Hofmann's method it yields trimethylamine. The formula deduced in this manner has been confirmed by synthesis. Hordenine was first synthesised by Barger [1] from phenylethyl alcohol, in the following stages :

$$C_6H_5.CH_2.CH_2.OH \xrightarrow{PCl_5} C_6H_5\ CH_2.CH_2.Cl \xrightarrow{(CH_3)_2NH} C_6H_5.CH_2.CH_2.N(CH_3)_2$$

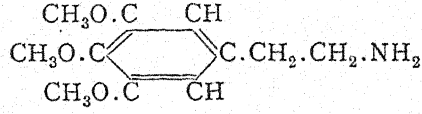
$$\xrightarrow{HNO_3} p\text{-}NO_2.C_6H_4.CH_2.CH_2.N(CH_3)_2 \longrightarrow NH_2.C_6H_4.CH_2.CH_2.N(CH_3)_2$$

$$\xrightarrow{HNO_2} \mathbf{HO}.C_6H_4.CH_2.CH_2.N(CH_3)_2$$

Phenolic bases of this type but of higher molecular weight, in which the $N(CH_3)_2$-groups are further removed from the benzene ring than in hordenine, have also been synthesised.[2] If the phenolic hydroxyl group is displaced from the para- to the ortho-position the physiological action is much weakened.[3]

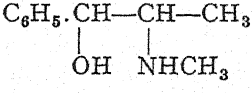
Anhaline and Mezcaline

From the cactus of the Anhalonium family, which grows in North America and is used by the natives as an intoxicant, a number of basic substances have been isolated, viz., *anhaline*, *mezcaline*, *anhalamine*, *anhalonidine*, *pellotine*, *anhalonine* and *lophophorine*. Most of these compounds are of unknown composition, although it seems probable from the work of E. Späth [4] that anhaline is identical with hordenine. The same investigator has synthesised **mezcaline** and shown it to possess the following structure [4] :



Späth has also suggested formulæ for other alkaloids of the anhalonium family, for which reference should be made to the original paper.

Ephedrine and Pseudo-ephedrine [5]



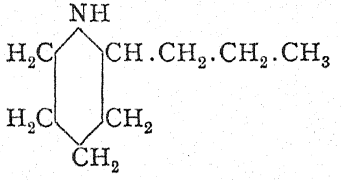
1 - Phenyl - 2 - methylaminopropane - 1 - ol.—Ephedrine and pseudo-ephedrine are two bases with mydriatic properties occurring in *Ephedra vulgaris*. They are optical isomerides, and under the influence of heat the former changes into the latter. Ephedrine is a white crystalline substance, which boils about 225° with decomposition. **Mydrine,** formed by the combination of ephedrine and homatropine (see p. 735), rapidly brings about a considerable degree of mydriasis and is employed medicinally for this purpose.

[1] Barger, *J. C. S.*, 1909, 95, 2193. [2] J. v. Braun and Deutsch, *Ber.*, 1912, 45, 2504. [3] J. v. Braun and O. Bayer, *Ber.*, 1924, 57, 913. [4] *Monats.*, 1919, 40, 129. C., 1919, III, 434. [5] E. Späth and G. Koller, *Ber.*, 1925, 58, 1268.

II.—ALKALOIDS OF THE PYRIDINE GROUP

Among the large number of alkaloids containing a pyridine nucleus only coniine, conhydrine, *pseudo*-conhydrine, γ-coniceïne, ricinine and piperine will be treated here.

α-Coniine, dextro-2-*n*-propyl-piperidine.



Coniine is of special interest from the historical standpoint, because the synthesis of this compound by Ladenburg, which was commenced in 1886 and finished at a later date, constituted the first complete synthesis of a naturally occurring alkaloid.[1] The reason for the early synthesis of the compound lies in its simple constitution. Of the numerous alkaloids known to-day, very few are built up from carbon hydrogen and nitrogen alone, and of these coniine possesses the simplest structure.

Coniine is present in hemlock, *Conium maculatum*, especially in the seeds, in which it is accompanied by N-methyl-coniine, γ-coniceïne, conhydrine, and pseudo-conhydrine. It is a colourless, very poisonous liquid, b.p. 167°.

Degradation of Coniine

A. W. Hofmann subjected coniine to certain reactions which he had previously carried out with piperidine, and found that the two compounds behaved in a similar manner.

1. *Exhaustive methylation* of coniine gave a product having the composition of a dimethyl-coniine, $C_8H_{15}(CH_3)_2N$, and also a hydrocarbon conylene, of the formula C_8H_{14}.

$$\underset{\text{Coniine.}}{C_8H_{17}N} \longrightarrow C_8H_{16}(CH_3)NCH_3I \longrightarrow C_8H_{16}(CH_3)NCH_3OH \xrightarrow{-H_2O}$$

$$C_8H_{15}(CH_3)_2N \longrightarrow C_8H_{15}(CH_3)_3N.OH \longrightarrow \underset{\text{Conylene.}}{C_8H_{14}} + N(CH_3)_3 + H_2O$$

Hofmann observed that conylene differed from piperylene by the same atomic complex, C_3H_6, as coniine from piperidine, and hence suggested that coniine might be a homologue of piperidine. Shortly afterwards, Königs put forward the surmise that coniine was a propyl-piperidine. This view was confirmed by Hofmann's distillation of the alkaloid with zinc dust.

2. The *distillation with zinc dust* was undertaken in the expectation of obtaining from coniine a compound richer in hydrogen. In actual practice it was found that hydrogen was removed [2] and the compound $C_8H_{17}N$ converted into one of the composition $C_8H_{11}N$. The new base, *conyrine*, was easily recognised as a derivative of pyridine, and being six

[1] *Ber.*, 1889, **22**, 1403. [2] Hofmann, *Ber.*, 1884, **17**, 825.

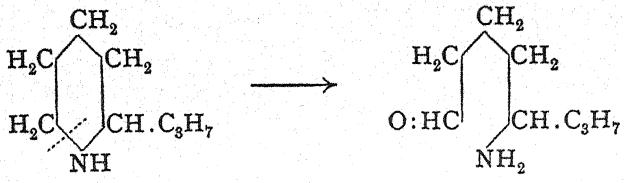
atoms poorer in hydrogen than coniine, appeared to stand to the latter in the same relationship as pyridine to piperidine.

Any doubt as to the nature of conyrine was resolved by its conversion into picolinic acid or 2-pyridine-carboxylic acid (see p. 682) on oxidation.

From this it followed that conyrine must be either 2-propyl- or 2-isopropyl-pyridine, and coniine therefore 2-propyl- or 2-isopropyl-piperidine. The choice between these two alternatives was decided in favour of the normal propyl structure by Hofmann's discovery that coniine, on reduction with hydriodic acid, gave ammonia and normal octane. Had an isopropyl group been present this could not have occurred without intramolecular rearrangement.

The constitution of coniine as 2-propyl-piperidine was finally confirmed by synthesis.

3. The *oxidation of coniine with hydrogen peroxide* led to the formation of δ-propyl-δ-aminovaleraldehyde [1] (δ-amino-*n*-octoic aldehyde).



Synthesis of Coniine

The synthesis of coniine was accomplished by Ladenburg [2] with the aid of the following three reactions: (*a*) introduction of side groups into pyridine by heating pyridine alkiodides under pressure (see p. 678); (*b*) condensation of α- and γ-methyl-pyridines with aldehydes (pp. 680 *et seq.*); (*c*) conversion of pyridines into piperidines by reduction with sodium and alcohol. The complete synthesis of coniine proceeds in the following stages:

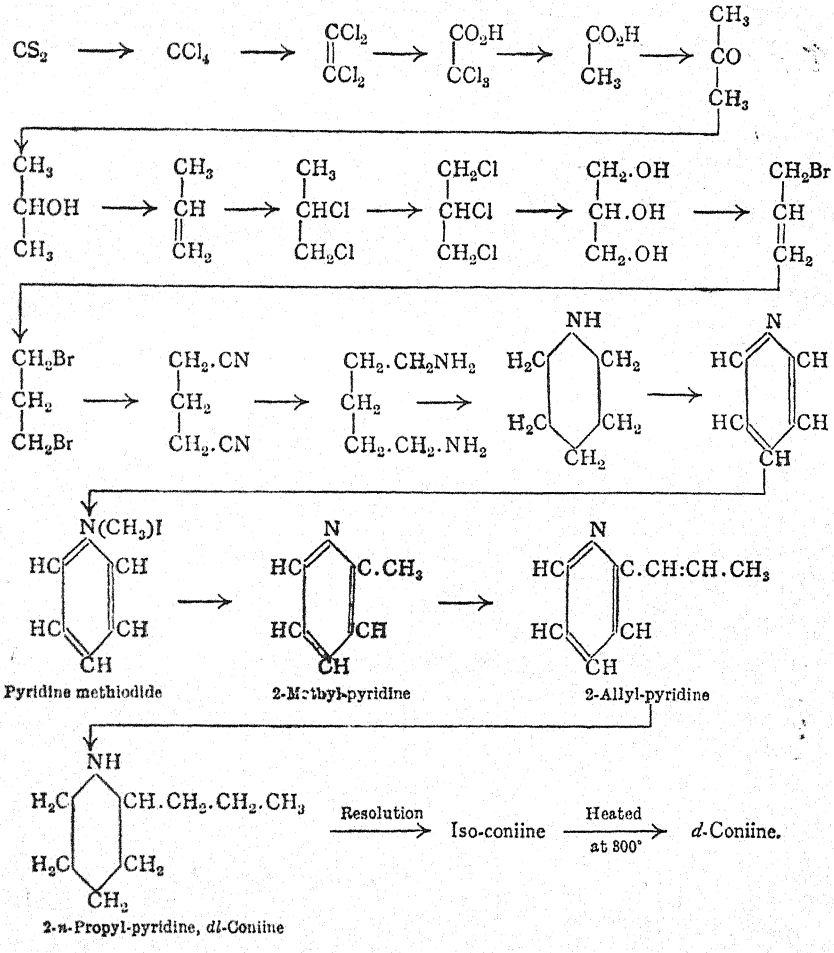
Carbon disulphide, which can be prepared from its elements, is converted through the various intermediate compounds shown below into trimethylene bromide. The latter, by way of trimethylene cyanide, yields pentamethylene diamine, from which piperidine is obtained by splitting off ammonia. Piperidine may be oxidised to pyridine, and this with methyl iodide gives the addition compound pyridine methiodide, which at 300° is transformed into the hydriodide of α-picoline. On heating picoline itself with paraldehyde to a high temperature it gives α-allyl-pyridine, which by reduction is converted into inactive coniine.

The racemic base may be resolved by means of *d*-tartaric acid. On crystallising a solution of *r*-coniine *d*-tartrate the first salt to separate is *d*-coniine *d*-tartrate, which is then removed and decomposed with alkali.

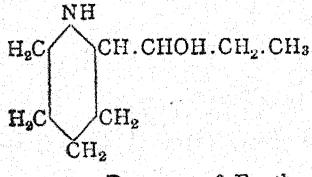
Synthetic coniine as thus obtained is identical in most respects with natural *d*-coniine, from which it differs mainly in possessing a slightly

[1] Wolffenstein, *Ber.*, 1895, **28**, 1460. Butyryl-butyric acid (δ-propyl-ketobutyric acid) is also formed. [2] *Ber.*, 1889, **22**, 1403; 1906, **39**, 2486. Compare also Lénart, *Ann.*, 1915, **410**, 95.

higher rotation (by about 4°). The synthetic product was at first believed to be an isomeric *iso*-coniine, which on heating alone or with alkali gave a product identical with the natural alkaloid. Recent work indicates that *iso*-coniine is merely an impure form of coniine.[1]



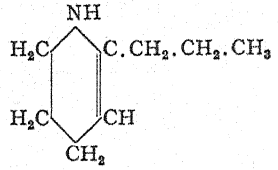
Conhydrine and **pseudo-conhydrine** are also present in plants of the hemlock family.[2] The former, m.p. 118° and b.p. 225° to 226°, crystallises from ether in colourless leaflets; the latter, m.p. 101° to 102° and b.p. 229° to 231°, is a deliquescent crystalline powder. A careful investigation of conhydrine has shown it to be an optically active 2-ethyl piperidyl-alkine[3] of the formula



[1] K. Hess and Weltzien, *Ber.*, 1920, 53**B**, 139. [2] For the separation of the alkaloid bases (coniine, methyl-coniine, γ-coniceïne, conhydrine, and pseudo-conhydrine) present in hemlock compare J. v. Braun, *Ber.*, 1905, **38**, 3708. [3] Löffler and Tschunke, *Ber.*, 1909, **42**, 929.

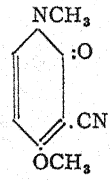
Pseudo-conhydrine is a hydroxy-coniine in which the hydroxyl group must be attached to the ring.[1]

γ-Coniceïne,

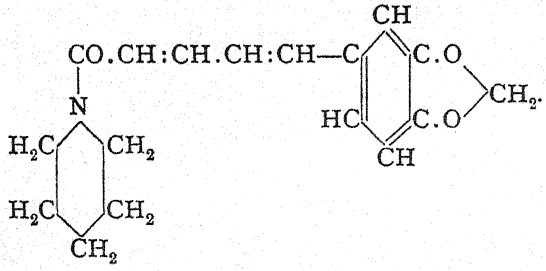


may be prepared directly from hemlock and also by synthesis.[2] Various structural isomerides of this substance, which cannot be described here, are obtained by the removal of the elements of water from conhydrine and pseudo-conhydrine, or of hydrogen iodide from their iodides.

Ricinine, the alkaloid of the castor oil plant, has the structure of a *1-methyl-3-cyano-4-methoxy-2-pyridone*.[3] This has been confirmed by synthesis.



Piperine,



The fruit and seeds of different species of pepper contain, in addition to a terpene, a comparatively large proportion (7 to 9 per cent.) of piperine. It was first discovered in 1819 by Oersted, and crystallises in monoclinic columns, m.p. 128° to 129°.

When boiled with alcoholic potash it breaks down into piperidine and piperic acid :

$$\underset{\text{Piperine}}{C_{17}H_{19}NO_3} + H_2O = \underset{\text{Piperidine}}{C_5H_{11}N} + \underset{\text{Piperic acid.}}{C_{12}H_{10}O_4}$$

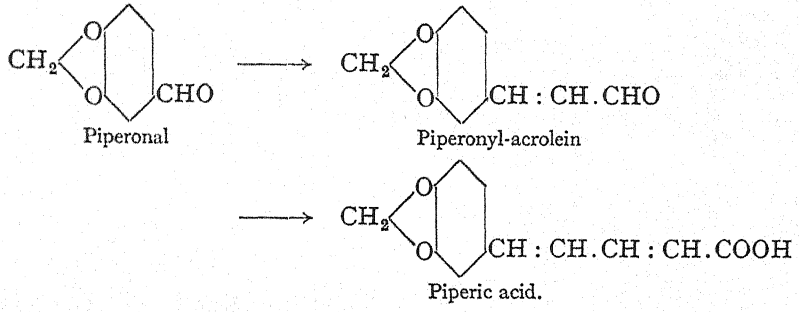
Hence it was concluded that piperine is a compound of amide type built up from piperidine and piperic acid. This view was confirmed by the partial synthesis of piperine [4] on heating piperidine in benzene solution with the chloride of piperic acid :

$$\underset{\text{Piperidine}}{C_5H_{10}NH} + \underset{\text{Piperic acid chloride}}{ClOC.C_{11}H_9O_2} = \underset{\text{Piperine.}}{C_5H_{10}N.OC.C_{11}H_9O_2} + HCl$$

The constitution and synthesis of piperidine have been described on pp. 677 *et seq.*, and the structure of piperic acid was solved by Fittig and confirmed by the following synthesis of Ladenburg and Scholtz.[5] Piperonal (see p. 443) was condensed with acetaldehyde in the presence

[1] Löffler, *Ber.*, 1909, **42**, 116. [2] S. Gabriel, *Ber.*, 1909, **42**, 4059. [3] E. Späth and G. Koller, *Ber.*, 1923, **56**, 880, 2454. [4] *Ber.*, 1892, **25**, 1390. *Ann.*, 1871, **159**, 142. [5] *Ber.*, 1894, **27**, 2858.

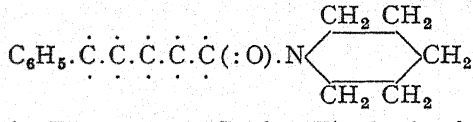
of aqueous alkali to give the unsaturated aldehyde, piperonyl-acrolein ; the latter was then converted into piperic acid by use of Perkin's reaction.



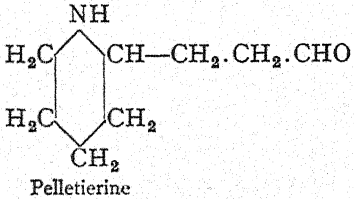
Piperonal — Piperonyl-acrolein — Piperic acid.

Consequently the above preparation of piperine from its hydrolysis products, piperidine and piperic acid, completes the synthesis of this alkaloid.

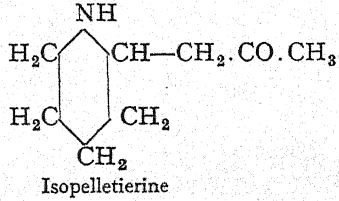
Owing to the rising price of pepper, experiments have been directed towards an artificial product of similar taste. An actual synthesis of piperine is out of the question owing to the cost of starting materials, but information as to the relationship between constitution and pepper-like taste has been gained by the work of H. Staudinger.[1] It appears that the molecule of piperine may undergo considerable changes without losing the characteristic taste. An essential condition is the acid amide linking of piperidine with a fatty-aromatic acid radical, and the most pronounced resemblance to pepper was observed with derivatives of δ-phenyl-*n*-valeric acid. The most effective structure is thus the following



Alkaloids of the Pomegranate Bark.—The bark of the pomegranate tree (*Punica Granatum* L.) contains several alkaloids, to the presence of which is due its long-known usefulness as a vermicide. These alkaloids, viz., *pelletierine* and *isopelletierine* of the formula $C_8H_{15}NO$, *methyl-isopelletierine* (*1-methyl-2-acetonyl-piperidine*) of the formula $C_9H_{17}NO$, and *pseudo-pelletierine*, $C_9H_{15}NO$, have been examined in detail by Hess, and later by Meisenheimer.[2] Their constitutions can now be regarded as established in accordance with the following formulæ :

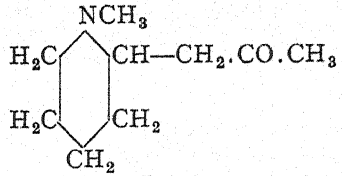


Pelletierine



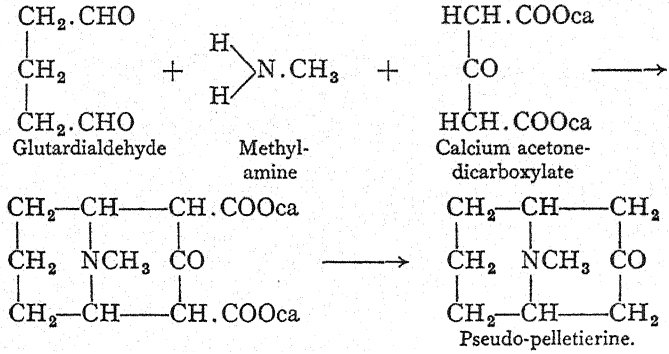
Isopelletierine

[1] H. Staudinger and co-workers, *Ber.*, 1923, **56**, 699, 711. H. Rheinboldt, *Ber.*, **56**, 1228. C. Riccomanni, *C.*, 1924, **II**, 339. [2] K. Hess and co-workers, *Ber.*, 1920, **53**, 129. *Ann.*, 1925, **441**, 101. J. Meisenheimer and E. Mahler, *Ann.*, 1928, **462**, 301.



Methyl-isopelletierine

Pseudo-pelletierine has recently been synthesised by Menzies and Robinson [1] in a simple manner from glutaric aldehyde as follows (compare synthesis of tropinone, p. 726) :



Glutardialdehyde — Methyl-amine — Calcium acetone-dicarboxylate

Pseudo-pelletierine.

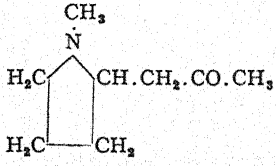
III.—ALKALOIDS OF THE PYRROLIDINE GROUP AND DERIVATIVES OF TROPANE

In this group are included hygrine and cuskhygrine, nicotine, atropine, hyoscyamine, cocaine, tropacocaine and others. Since the five-membered pyrrolidine ring is more easily formed than the corresponding six-membered ring, the production of alkaloids of the pyrrolidine type in plants is not surprising. In all probability a number of other alkaloids, the constitution of which is still unknown, will eventually be found to fall within this class.

Hygrines

From South American coca, obtained from truxillo and cusko leaves, Liebermann [2] succeeded in isolating two bases, hygrine ($C_8H_{15}NO$) and cuskhygrine ($C_{13}H_{24}N_2O$). Both of these are amino ketones, which on oxidation with chromic acid are converted into hygrinic acid (*cf.* p. 619).

Hygrine, 1-*methyl-2-acetonyl-pyrrolidine*, possesses the following structure :



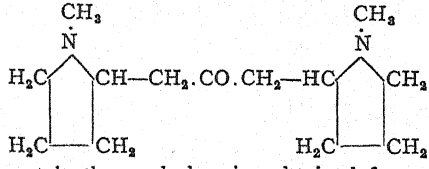
which is confirmed by the formation of a monoxime, the degradation of hygrine to hygrinic acid (1-methyl-pyrrolidine-2-carboxylic acid) and by the synthesis of the base.[3]

[1] R. C. Menzies and R. Robinson, *J. C. S.*, 1924, **125**, 2163. [2] C. Liebermann and Giesel, *Ber.*, 1897, **30**, 1113. K. Hess, *Ber.*, 1913, **46**, 3113, 4104. [3] *Ber.*, 1900, **33**, 1161.

Hygrine is found more particularly in Peruvian cusko leaves, in which it occurs up to 0·2 per cent. It is a liquid which darkens in air and boils at 193° to 195° under ordinary pressure.

Cuskhygrine

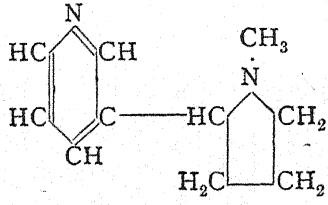
Cuskhygrine, $C_{13}H_{24}N_2O$, is simply related to hygrine, $C_8H_{15}NO$, one hydrogen atom of the latter being replaced by the monovalent 1-methyl-pyrrolidine radical. It conforms in all probability to the structure [1]



Cuskhygrine is present in the crude hygrine obtained from cusko leaves, of which it constitutes the higher boiling main fraction. It is a colourless oil of faint odour, boiling at 185° under 32 mm. pressure.

Nicotine

1-*Methyl*-2-*β*-*pyridyl*-*pyrrolidine*,



Nicotine is found combined with malic acid and citric acid in the leaves of tobacco (*Nicotiana tabacum*).

The above constitutional formula was advanced by Pinner in 1893, and finally confirmed by the synthesis of the alkaloid by A. Pictet.[2]

Synthesis of Nicotine [2]

Starting from *β*-aminopyridine, the synthesis of nicotine involved the following eight changes :

β-Aminopyridine —(distillation with mucic acid)→

1-*β*-Pyridyl-pyrrole —(strongly heated)→

2-*β*-Pyridyl-pyrrole —(potass. salt with CH_3I)→

1-Methyl-2-*β*-pyridyl-pyrrole methiodide —(distillation with lime)→

1-Methyl-2-*β*-pyridyl-pyrrole (nicotyrine) —(action of I)→

Iodo-nicotyrine (1-methyl-2-*β*-pyridyl-4-iodopyrrole) —(reduction)→

Dihydro-nicotyrine (1-methyl-2-*β*-pyridyl-pyrroline) —(red. of the perbromide with Sn and HCl)→

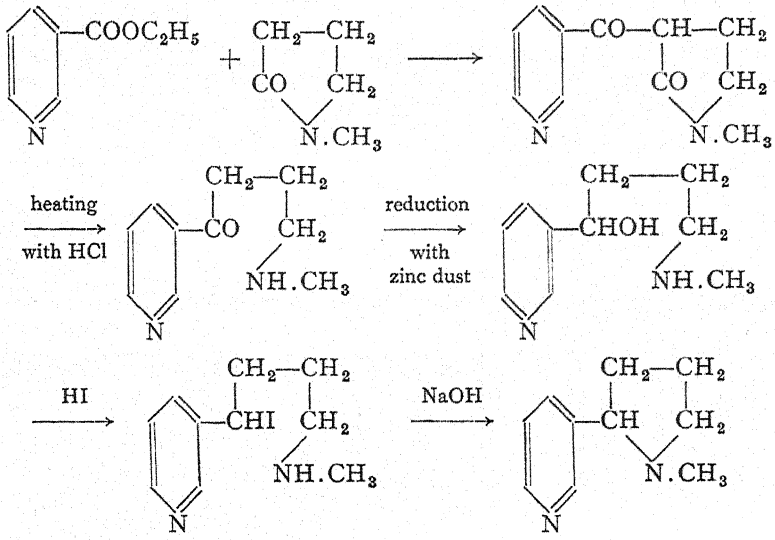
Tetrahydro-nicotyrine (*dl*-nicotine) —(resolution with tartaric acid)→

l-Nicotine.

[1] See *Ann. Rep. Chem. Soc.*, 1925, p. 134.

[2] Pictet and Rotschy, *Ber.*, 1904, **37**, 1225.

A further synthesis was subsequently effected by E. Späth and H. Bretschneider [1] in the following stages :



Note.—The first condensation in this synthesis is brought about in the presence of sodium ethoxide, giving a product which, on being heated with fuming hydrochloric acid, is hydrolysed with loss of carbon dioxide.

l-Nicotine

The naturally occurring alkaloid is laevorotatory, $[a]_D^{20} = -166{\cdot}4°$, and, as indicated above, can also be obtained by resolving the synthetic *dl*-nicotine with the aid of tartaric acid. According to the kind of tobacco, the nicotine content varies from 0·6 to 8 per cent. (pipe tobacco 0·518 to 0·854 per cent., cigars 0·801 to 2·887 per cent.). In general the finer kinds of tobacco contain smaller proportions of nicotine.

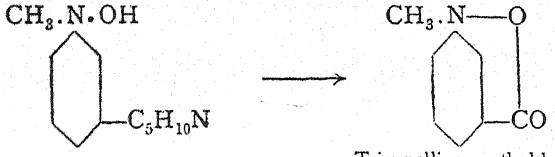
The alkaloid is conveniently obtained from extract of tobacco, which is prepared industrially by extracting a raw tobacco of high nicotine content with cold water and concentrating the solution. The extract is used for the impregnation of chewing tobacco, and contains about 8 to 10 per cent. of nicotine. It is first diluted with water, and freed from hydrocarbons by the addition of acid and extraction with ether. The solution is then made alkaline, and the free nicotine repeatedly extracted with ether.

Freshly prepared *l*-nicotine is a colourless oil, which dissolves readily in water, has a burning taste, and is very poisonous. When pure, it has an unpleasant, stupefying odour, unlike that of tobacco. It can only be distilled without decomposition *in vacuo* or in a current of hydrogen ; in air it rapidly turns brown and resinifies. Nicotine boils at 246·2° under 730 mm. pressure. It forms diacid salts which do not crystallise

[1] *Ber.*, 1928, 61, 327.

well ; these dissolve readily in water and rotate the plane of polarisation to the *right.*

Nicotine yields two *mono-methiodides.*[1] One of these isomerides is obtained as a syrupy mass on bringing together equimolecular amounts of nicotine and methyl iodide. The second results when nicotine is first treated with a molecular equivalent of hydriodic acid and then with methyl iodide : under these conditions the methyl iodide unites with the less basic nitrogen atom of the pyridine ring. By converting the methiodide into the hydroxide and oxidising the latter with potassium permanganate, Pictet [1] obtained the alkaloid *trigonelline*, which is present in the seeds of *fenugreek*, of *Strophanthus hispidus*, and other plants.



Trigonelline, methyl-betaine of nicotinic acid.

Conversion of l-*Nicotine into* dl-*Nicotine*

As has already been stated in the general section of this book, a number of optically active compounds can be racemised or transformed into their inactive modifications by continued heating in solution.

This phenomenon has also been observed in the case of nicotine.[2] On heating an aqueous solution of the monohydrochloride or sulphate of nicotine at 180° to 250° in a sealed tube, the rotation steadily diminishes and finally becomes zero.

dl-Nicotine may be isolated from heated solutions of its salts in the usual manner. In properties such as boiling-point, specific gravity, refractive index, smell, solubility and salt formation, it is identical with the natural *l*-rotatory alkaloid.

d-*Nicotine* [3]

This was isolated in the crude state during the preparation of *l*-nicotine from the inactive synthetic compound, and purified by use of *l*-tartaric acid. Its specific rotation $[\alpha]_D^{20}$ was found to be $+163{\cdot}17°$, and in boiling-point and other physical properties it was identical with the *l*-isomeride.

d-Nicotine is less poisonous than *l*-nicotine. In this respect, the different action of the two antipodes towards the animal organism may be compared to the different behaviour of optical antipodes in general towards any other optically active compound, and towards organised, as distinct from unorganised, ferments.

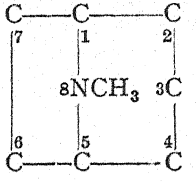
In addition to nicotine, the alkaloids [4] *nicoteine*, *nicotimine*, and *nicotelline* have been isolated from the tobacco plant.

[1] Pictet and Genequand, *Ber.*, 1897, **30**, 2117. [2] Pictet and Rotschy, *Ber.*, 1900, **33**, 2353.
[3] Pictet and Rotschy, *Ber.*, 1904, **37**, 1232. [4] Pictet and Rotschy, *Ber.*, 1901, **34**, 696. *Compt. rend.*, **132**, 971.

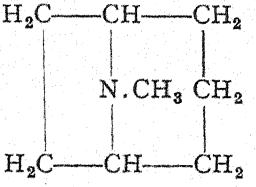
Compounds of the Tropane Series

Nomenclature.—The various alkaloids of this group contain a peculiar combination of a reduced pyrrole and a reduced pyridine ring (Willstätter), the periphery of the cyclic system forming a seven-membered carbon ring :

I.



II.



Derivatives of tropane are generally described by use of the numbering given in formula I, the compounds being referred in the customary manner to tropane (II) as parent substance.

In the following list are given the older names in common use for the more important members of this group, together with the systematic names referred to tropane.

Hydro-tropidine . .	$C_8H_{15}N$ . . .	tropane
Tropine	$C_8H_{14}(OH)N$ . .	tropanol
Tropinone . . .	$C_8H_{13}ON$ . . .	tropanone
Tropigenine . . .	$C_7H_{13}ON$ . . .	nortropanol
Norhydro-tropidine . .	$C_7H_{13}N$ . . .	nortropane
Tropidine . . .	$C_8H_{13}N$ . . .	tropene

Willstätter's [1] syntheses of tropane and tropane derivatives are based upon the alkylating action of a halogenated group on a basic group of the same molecule. Just as an alkyl halide reacts with a primary amine to yield the salt of a secondary amine, or with a tertiary amine to form a quaternary ammonium salt, so with a halogenated base an intramolecular reaction may occur between the halogenated portion of the molecule and the basic group. In such a case the halogen atom and the alkyl residue to which it was originally united become attached by separate valency bonds to the nitrogen atom, leading to the production of a cyclic base in which nitrogen forms part of the ring. Thus a halogenated primary base yields the salt of an imine, and a tertiary compound yields a quaternary ammonium halide. A reaction of this type is described by Willstätter as *intramolecular alkylation* (compare the synthesis of 2-methyl-1-dimethyl-pyrrolidinium chloride from pentenyl-dimethylamine, p. 618).

Intramolecular alkylation may also lead to the formation of dicyclic bases, if the addition products of certain unsaturated monocyclic amines are used as starting material.

Derivatives of tropane have been synthesised in this manner by Willstätter, starting from a base containing a cyclic system of seven carbon atoms, and having a halogen atom in one of the two δ-positions (*i.e.* positions 4 or 5) to the N-group (see below).

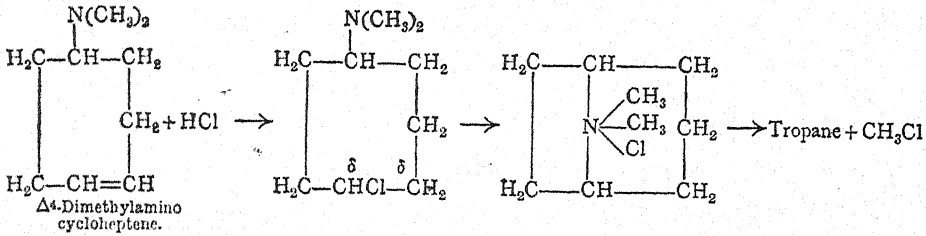
Tropane, hydro-tropidine (formula II, above), the parent substance of the tropane series, was first obtained by Ladenburg by the action of zinc dust and hydrochloric acid on tropine iodide :

$$C_8H_{14}IN, HI + 2H = C_8H_{15}N, HI + HI$$

[1] *Ann.*, 1901, 317, 307.

According to Willstätter, tropane is best prepared from the hydrogen halide addition products of tropidine, by reduction with zinc dust and hydrogen iodide in the cold. It is also formed from tropinone by treatment with zinc dust and hydriodic acid.

Willstätter [1] has synthesised tropane by two methods. One of these starts from the addition compound obtained by union of Δ^4-dimethyl-amino-cycloheptene with hydro-

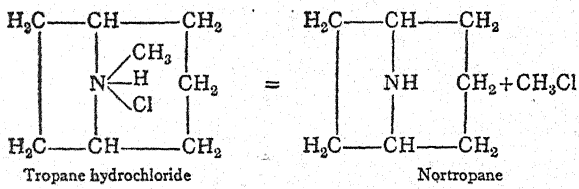


chloric acid. When this is gently warmed it is largely converted by intramolecular ammonium salt formation into tropane methochloride, from which, on dry distillation, tropane is obtained. It is a liquid of boiling-point 167°, which is sparingly soluble in cold, and still less soluble in hot water.

On exhaustive methylation tropane yields hydro-tropilidene or cyclo-heptadiene, C_7H_{10}, the final stage of the degradation being as follows :

$$C_7H_{11}N(CH_3)_3OH = C_7H_{10}+N(CH_3)_3+H_2O$$

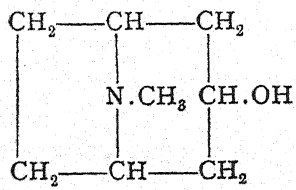
Nortropane, norhydro-tropidine, $C_7H_{13}N$, is formed by distilling tropane in a stream of hydrochloric acid, when the N-methyl group is removed as methyl chloride (Ladenburg).



Tropane hydrochloride Nortropane

Nortropane is a transparent crystalline substance, boiling about 161° and melting about 60°. *When distilled with zinc dust it yields 2-ethylpyridine*, a reaction which first led to the discovery that tropine contains a pyridine nucleus.

Tropine, tropanol,



Tropine, the basic cleavage product of most of the Solanaceæ alkaloids (*e.g.* atropine), is one of the most important derivatives of tropane. It has been more completely investigated than any of the other derivatives, with results which gave the first insight into the structure of the tropane ring.

Formation and Properties of Tropine

Tropine was first obtained by the hydrolysis of atropine with barium hydroxide (Kraut, 1863), and was later isolated in a similar manner from hyoscyamine (Ladenburg) and belladonnine (Merling). Willstätter

[1] *Ann.*, 1901, 317, 315.

prepared tropine by the reduction of tropinone,[1] and finally effected its synthesis.

The base, which is optically inactive, crystallises from absolute ether in large plates, m.p. 63°, and b.p. 229°. It dissolves readily in water and alcohol, giving solutions with a strong alkaline reaction.

ψ-Tropine, described later, is a geometrical isomeride of tropine.

Constitution of Tropine

The following are the main points from which the constitution of tropine has been deduced.

Proof of the presence of an alcoholic hydroxyl group in tropine is based on the transformation of the latter into tropidine by simple removal of water. Since tropine is a tertiary base, and thus contains no hydrogen attached to nitrogen, it must be the hydrogen of this hydroxyl group which is replaced by an acidic radical in the alkaloid atropine.

That tropine contains a pyridine nucleus follows from the conversion of tropidine into dibromo-pyridine and α-ethyl-pyridine.

The presence of a seven-membered carbon ring in tropine is shown by the conversion of tropidine into tropilidene or cycloheptatriene on exhaustive methylation,[2] and also by the degradation of tropinic acid to normal pimelic acid [3] (see p. 620).

Willstätter has conclusively proved the existence of a pyrrolidine nucleus in tropine by an examination of the degradation products formed on oxidation. Tropinic acid was identified as 1-methyl-pyrrolidine-2-carboxylic-5-acetic acid, and by energetic oxidation was converted into N-methyl-succinimide (p. 621). In this manner the pyrrolidine nucleus was isolated from tropine in a simple, well-known form.

In establishing the above formula for tropine, a factor of importance was the observation that tropinone, the primary oxidation product of tropine, readily yields a dibenzal-compound and a di-isonitroso derivative, and must therefore contain the group $CH_2.CO.CH_2$.

Synthesis of Tropine

Willstätter's synthesis of tropine is divided into two parts: the synthesis of tropidine and its conversion into tropine.

(a) *Synthesis of Tropidine*

This synthesis has been effected in two ways, only one of which is described here.[4]

In the main this is a reversal of the stages by which tropine may be degraded to an unsaturated hydrocarbon containing a ring of seven

[1] Willstätter and Iglauer, *Ber.*, 1900, 33, 1170. [2] Merling, *Ber.*, 1891, 24, 3110.
[3] Willstätter, *Ber.*, 1898, 31, 1534, 1542. [4] Willstätter, *Ann.*, 1901, 317, 307.

carbon atoms. The starting-point is suberone, obtained from suberic acid, and the synthesis proceeds in the following steps :

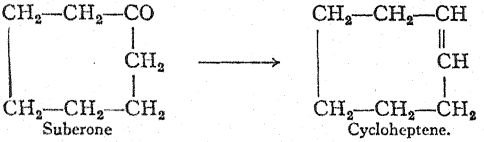
1. Suberone is converted into cycloheptene and thence into cycloheptadiene and cycloheptatriene.

2. Cycloheptatriene is converted into dimethylamino-cycloheptadiene, which is then reduced to dimethylamino-cycloheptene.

3. The hydrogen halide addition product of this monocyclic tropine base is transformed into a dicyclic tropane-methyl-ammonium salt, which on distillation yields tropidine.

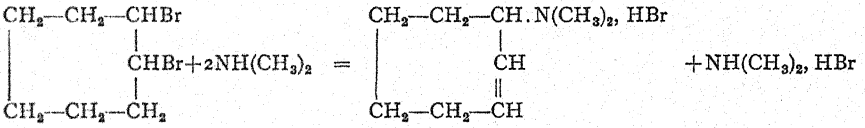
1. *Synthesis of Cycloheptatriene*

Suberic acid, which can be obtained from glutaric acid by the electrolytic method of Crum Brown and Walker, is converted into the calcium salt and distilled. The *suberone*, or cycloheptanone, prepared in this way is first converted into the hydrocarbon *cycloheptene*, containing one double bond :

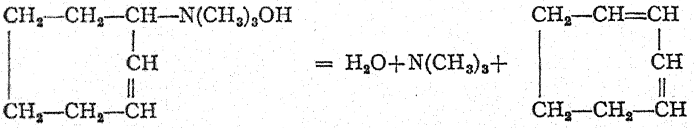


This can be accomplished either by treating suberyl iodide with alcoholic potash (Markownikoff), or by the exhaustive methylation of suberylamine (aminocycloheptane) obtained by the reduction of suberone oxime (Willstätter).

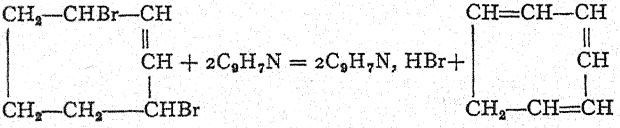
A second double bond is introduced into the molecule by allowing cycloheptene dibromide, dissolved in indifferent solvents, to react with dimethylamine. In this manner an unsaturated Δ^2-*dimethylamino-cycloheptene* is formed, according to the equation :



This base may be converted into the quaternary ammonium hydroxide, which on distillation decomposes into trimethylamine and *cycloheptadiene*.



The dibromide of cycloheptadiene can be converted into cycloheptatriene by various methods. When heated with quinoline, for example, hydrogen bromide is removed and a quantitative yield of cycloheptatriene is obtained.



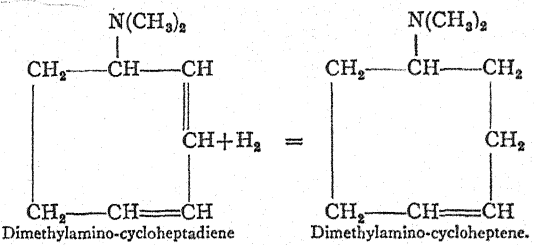
The synthetic cycloheptatriene produced in this way from suberone is identical in all respects with the tropilidene prepared from tropine.

2. *Conversion of Cycloheptatriene into Tropidine*

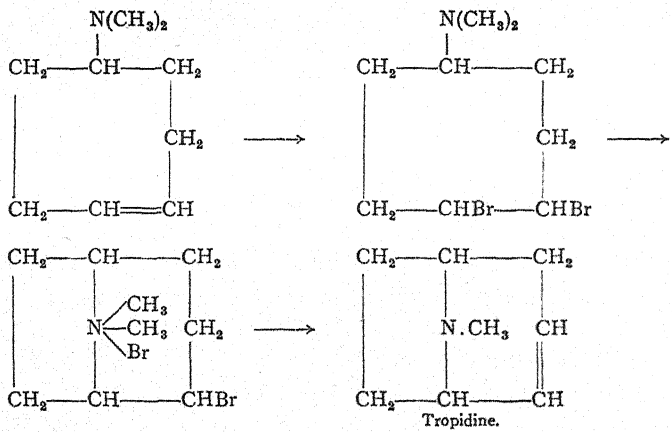
Cycloheptatriene hydrobromide, which is formed by treating the hydrocarbon in the cold with one molecular proportion of hydrogen bromide, reacts readily at ordinary

temperatures with dimethylamine in benzene solution, with the production of *dimethylamino-cycloheptadiene.*

When the latter is reduced with sodium in alcoholic solution it passes into dimethylamino-cycloheptene, the doubly unsaturated base taking up two atoms of hydrogen, according to the equation:



Dimethylamino-cycloheptene in acid solution adds on bromine to form a dibromide, which, on being warmed, rapidly undergoes rearrangement into 4-bromotropane-methylammonium bromide. Under the influence of alkali this substituted ammonium salt readily decomposes into hydrobromic acid and tropidine-methyl-ammonium bromide. When the latter is converted into the chloride and submitted to dry distillation it yields tropidine.



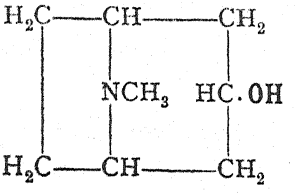
(b) *Conversion of Tropidine into Tropine*

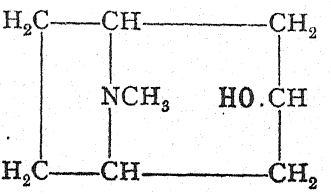
Tropidine may be converted into *ψ*-tropine by way of its hydrogen bromide addition compound, 3-*bromotropane.* When this is heated to 200° with sulphuric acid in a sealed tube it yields *ψ*-tropine (Willstätter).

Since *ψ*-tropine can be transformed into *tropine* (see below), the series of reactions just described constitutes a complete synthesis of tropine, and therefore also of the solanine alkaloids *atropine*, *atropamine*, *belladonnine*, and *hyoscyamine*, and the coca alkaloids *tropacocaine* and *r-cocaine*. This is treated in more detail under the individual alkaloids.

ψ-Tropine, pseudotropine, has the same constitution as its isomeride tropine, the relationship between these compounds being of the *cis- trans-* type, similar to that existing between borneol and isoborneol (see pp. 483

et seq.). Further examples of the same kind will be met with in the tropane series. The relationship may be illustrated by the following space formulæ:

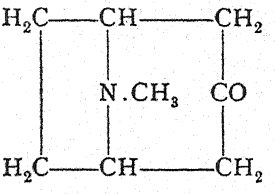




ψ-Tropine boils at 240° to 241°, and crystallises in needles of melting-point 108°. It is optically inactive, and readily dissolves in alcohol and water to give strongly alkaline solutions. The base can be identified and separated from tropine by means of its *picrate*,[1] $C_8H_{15}NO$, $C_6H_2(NO_2)_3OH$.

ψ-Tropine was discovered at a much later date than tropine and is less readily prepared. It can be obtained from the latter in two ways, viz., directly, by heating it with a solution of sodium ethoxide, and indirectly, by oxidation to tropinone and reduction with sodium and alcohol.[2] Conversely, ψ-tropine may be converted into tropine by oxidation to tropinone followed by reduction with zinc dust and hydriodic acid.[3] As already mentioned, the last reaction is a vital link in the synthesis of tropine and alkaloids derived from it.

Tropinone (Tropanone)



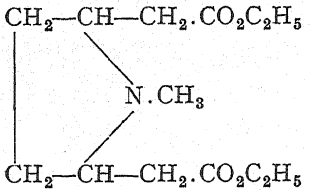
Tropinone is the ketone corresponding to the alcohol tropine. It was obtained simultaneously by Willstätter and by Ciamician and Silber by the oxidation of tropine with chromium trioxide in glacial acetic acid solution, and results in a similar manner from ψ-tropine and from ecgonine. On further oxidation it yields tropinic acid.

Tropinone melts at 41° to 42°, boils at 224° to 225°, and crystallises in long flat needles. It is strongly basic, and displaces ammonia from ammonium salts. Its vapour forms white fumes with hydrochloric acid gas.

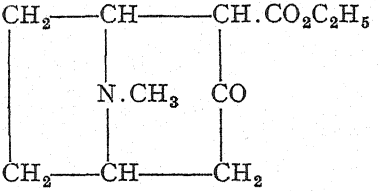
The following *synthesis of tropinone* was carried out by Willstätter.[4] N-Methylpyrrole-2 : 5-diacetic ester is reduced with hydrogen in presence of oxygenated platinum black to give N-methylpyrrolidine-2 : 5-diacetic ester[5] (I). The latter with sodium ethoxide undergoes intramolecular

[1] Willstätter, *Ann.*, 1903, **326**, 41. [2] Willstätter, *Ber.*, 1896, **29**, 936. [3] *Ber.*, 1910, **33**, 1170. [4] Willstätter and Bommer, *Ann.*, 1921, **422**, 15. [5] Willstätter and Jaquet, *Ber.*, 1918, **51**, 767.

acetoacetic ester condensation to form tropinone carboxylic ester (II), which on warming with dilute mineral acids gives tropinone.

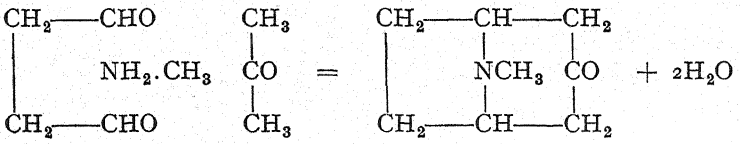


I.

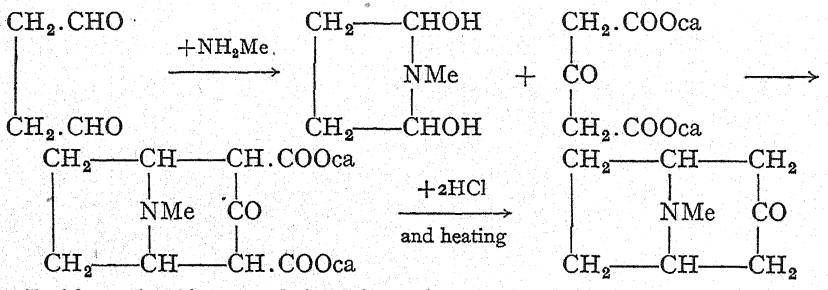


II.

Robinson's synthesis of tropinone.—A remarkably simple synthesis of tropinone has been devised by Robinson.[1] Succindialdehyde—prepared from succindialdoxime and nitrous fumes—was allowed to interact in aqueous solution with acetone and methylamine. After the lapse of half an hour at the ordinary temperature tropinone was found to be present.



In an experiment in which the calcium salt of acetone dicarboxylic acid was employed in place of acetone, a yield of tropinone amounting to 42 per cent. of the theory was obtained. The tropinone dicarboxylate first formed readily parts with two molecules of carbon dioxide on being heated in acid solution.



Robinson's Theory of the Phytochemical Synthesis of certain Alkaloids.[2]—The synthesis of tropinone described above proceeds with such ease that Robinson has suggested that similar reactions probably occur in the plant. All new carbon to carbon links are assumed to result from (1) an aldol condensation, or (2) the closely related condensation between a compound containing the group : CH.CO. and a carbinol-amine having the group : C(OH).N :, products of the latter type being readily obtained by union of an aldehyde or ketone with ammonia or an amine (see II).

The essential starting points in the plant synthesis may be ammonia and formaldehyde, amino-acids such as ornithine or lysine, and certain degradation products of carbohydrates. For example, formaldehyde is

[1] Robinson, *J. C. S.*, 1917, **111**, 762. [2] R. Robinson, *J. C. S.*, 1917, 876.

known to exert a combined methylating and oxidising action on ornithine, leading to the loss of ammonia and carbon dioxide and the formation of a base which may undergo cyclisation to give a carbinol-amine (I) derived from pyrrolidine :

$$NH_2.CH_2.CH_2.CH_2.CHNH_2.CO_2H + CH_2O \longrightarrow NHMe.CH_2.CH_2.CH_2.CHO + NH_3 + CO_2$$

I. $CH_2.CHOH$ / $CH_2.CH_2$ > NMe ⟵

Further interaction with formaldehyde is supposed to attack both ends of the amino-acid molecule, yielding succindialdehyde and methylamine, which combine to form the dihydroxy base II.

$$NH_2.CH_2.CH_2.CH_2.CHNH_2.CO_2H + 2CH_2O \longrightarrow OHC.CH_2.CH_2.CHO + 2MeNH_2 + CO_2$$

$CH_2.CHO$ / $CH_2.CHO$ $+ H_2N.Me \longrightarrow$ $CH_2.CHOH$ / $CH_2.CHOH$ > NMe II.

Among carbohydrate disruption products, citric acid is suggested as providing acetone residues in the form of acetone-dicarboxylic acid. Alternatively, the latter compound is known to be produced *in vitro* from other sources, *e.g.* by the spontaneous decomposition of calcium trisaccharate.[1]

Condensation is then assumed to proceed along the following lines, according to which one molecule of acetone-dicarboxylic acid reacts with either one or two molecules of the base I. Subsequent elimination of carbon dioxide leads in the former case to **hygrine** (III), and in the latter to **cuskhygrine** (see p. 717).

NMe / H_2C $CHOH$ / H_2C CH_2 + $COOH$ / $CH_2.CO.CH_2.COOH$ ⟶

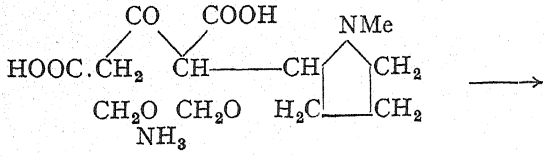
NMe $COOH$ / H_2C $CH.CH.CO.CH_2.COOH$ / H_2C CH_2 IV. ⟶ NMe / H_2C $CH.CH_2.CO.CH_3$ / H_2C CH_2 III.

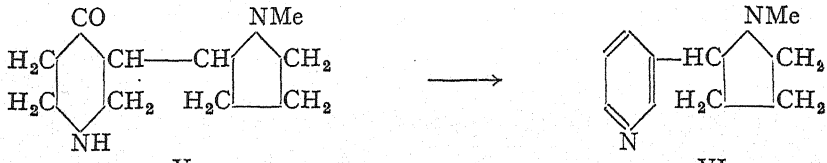
On the other hand, from the base II tropinone has already been synthesised in a similar manner, as described on p. 726. Tropinone by further simple changes in the plant may give rise to **tropine, ψ-tropine, hyoscyamine** and **atropine.**

Nicotine (VI) may be derived from IV, the immediate precursor of hygrine, by interaction with formaldehyde and ammonia, accompanied by loss of carbon dioxide. The ketonic ring in V is assumed to undergo reduction (CO → CHOH) followed by dehydration (. $CH_2.CHOH.CH<$ → . $CH_2.CH:C<$) and subsequent oxidation to the aromatic state.

[1] Lippmann, *Ber.*, 1893, **26**, 3057.

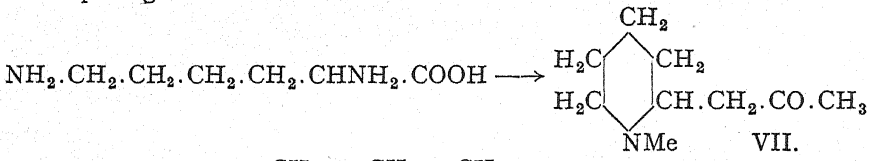
This mechanism clearly explains the β-attachment of the pyrrolidine ring to the pyridine nucleus.



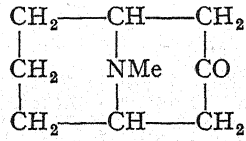


V. VI.

Piperidine derivatives would be expected to result by similar changes from the amino-acid lysine, which with formaldehyde should yield the **methyl-pelletierine** VII and **ψ-pelletierine** (VIII). Both of these occur in the pomegranate tree.



VII.



VIII.

Robinson comments on the frequent occurrence in the same natural source of a number of closely related alkaloids, as in the case of the pelletierines or of coniine and its associates. These variations, it is suggested, are produced from a primary product by alternate hydration and dehydration, or by oxidation and reduction. As an illustration it is observed that Hess [1] has shown that the base VII reacts with formaldehyde in such a way that nitrogen is demethylated and the ketone reduced to the carbinol. The resulting compound on further reduction ($CHOH \rightarrow CH_2$) would yield **coniine** having the side chain $CH_2.CH_2.CH_3$; or by dehydration followed by hydration **conhydrine** might be formed ($CH_2.CHOH.CH_3 \rightarrow CH:CH.CH_3 \rightarrow CHOH.CH_2.CH_3$). Similar considerations are advanced to account for the synthesis of other types of alkaloids, including *sparteine*, *cinchonine*, *hydrastine*, *narcotine*, *morphine* and *thebaine*.

Mention has already been made of the existence of a number of derivatives of tropinone which point to the latter containing the group $CH_2.CO.CH_2$ (see p. 722). These cannot be described further, but from their occurrence it followed that tropine contained the group CH_2.

[1] *Ber.*, 1917, **50**, 531.

$CHOH.CH_2$, and also, when other facts were taken into account, a pyrrolidine ring. Hence Willstätter's investigations on tropinone derivatives had an important bearing on the constitution of tropine, as well as on that of atropine, cocaine and other alkaloids.

Behaviour of Tropinone on Reduction.[1]—The best results were obtained by reducing tropinone in the cold with zinc dust and hydriodic acid (sp. gr. 1·7 to 1·96). In this way a good yield of tropine, together with a smaller amount of ψ-tropine, was isolated. Since tropinone can be obtained by the oxidation of ψ-tropine, it is thus possible to pass from ψ-tropine through tropinone into tropine, a change which cannot be effected in any other manner, and which has been of value in connection with the synthesis of tropine, atropine and other compounds.

Tropinone has also been obtained by the oxidation of ecgonine, a hydrolysis product of cocaine and tropacocaine. The reduction of the ketone to tropine therefore makes it possible to convert tropacocaine or cocaine into atropine.

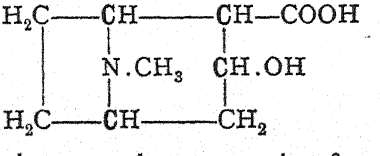
Cocaine ——> ecgonine ——> tropinone ——> tropine ——> atropine.

It should be mentioned, however, that the relationship between cocaine and atropine had been shown much earlier by Einhorn, by the conversion of anhydro-ecgonine into tropidine (see anhydro-ecgonine).

The reduction of tropinone with zinc dust and hydriodic acid, even at very low temperatures, proceeds beyond the formation of the alcohol base and finally yields tropane.

When reduced with sodium in moist ethereal or in alcoholic solution, tropinone is converted into ψ-tropine, the same result being obtained by use of sodium amalgam in weakly acid solution.[2]

Ecgonines, 3-Hydroxytropane-2-Carboxylic Acids



Ecgonine, as will be seen above, contains four asymmetric carbon atoms and should therefore exist in 16 optically active forms. As, however, the $—CH_2.CH_2—$ bridge united to the piperidine ring can only be attached in the *cis*-position, the number of possibilities is reduced to 8. So far only two of these are known, viz., ordinary *l*-ecgonine and the *d*-ecgonine (*d*-pseudoecgonine) produced from it by the action of alkali. To these must be added synthetic, optically inactive *r*-ecgonine. The *l*- and *d*-ecgonines already known are not optical antipodes, but possess specific rotations of different magnitudes. If we recall the behaviour of inactive tropine and ψ-tropine towards alkalis, it seems highly probable that *l*-ecgonine corresponds to the alkali-labile tropine, and *d*-ecgonine

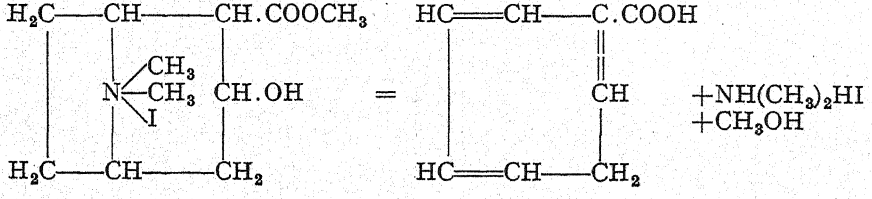
[1] Willstätter and Iglauer, *Ber.*, 1900, 33, 1172. *Ann.*, 1903, 326, 41. [2] Willstätter, *Ber.*, 1896, 29, 936.

to the alkali-stable geometrical isomeride ψ-tropine. The structural difference probably depends on the relative positions of the hydroxyl and N-methyl groups. In accordance with a proposal of Willstätter,[1] it might be more satisfactory to extend the above nomenclature by describing dextrorotatory ecgonine as *d*-ψ-ecgonine, in distinction to ordinary or *l*-ecgonine; or, in general, by dividing the ecgonines and the cocaines derived from them into the ecgonine series and the pseudoecgonine series, according to the orientation of the hydroxyl group.

***l*-Ecgonine,** $C_9H_{15}NO_3+H_2O$, is the more interesting of the optically isomeric ecgonines, since from it is derived the important alkaloid *l*-cocaine (methyl ester of benzoyl-ecgonine).

Constitution of Ecgonine.—The presence of a pyridine ring in ecgonine was established by Stoehrs, who obtained α-ethyl-pyridine by distilling the alkaloid with zinc dust. The structural similarity between tropine and ecgonine, *i.e.*, their derivation from the same parent substance, followed from Einhorn's discovery that when anhydro-ecgonine is heated to 280° with hydrochloric acid it decomposes into carbon dioxide and tropidine (p. 732). This result was also deduced from the researches of Liebermann, who converted ecgonine by oxidation with chromic acid into *d*-tropinic acid and ecgoninic acid. In this reaction tropinone occurs as an intermediate product. The varying opinions as to the constitution of tropine have therefore also had their reflections on that of ecgonine. Definite proof that the hydroxyl group occupies the same position in ecgonine as in tropine, and that the carboxyl group is attached to a neighbouring carbon atom, as indicated in the above formula, was supplied by the work of Willstätter and Müller.[2] It was found that on gentle oxidation with chromic acid ecgonine could be converted into tropinone, *i.e.*, into the ketone which is the primary oxidation product of tropine and ψ-tropine; and further, that the behaviour of ecgonine was not that of an α- or γ-hydroxy acid. Hence the carboxyl and hydroxyl groups must occupy the β-position to one another, and ecgonine is therefore a β-carboxylic acid of tropine. Its degradation to N-methylsuccinimide has already been described on p. 621.

When warmed with alkalis, the methiodides of *l*-, *d*- and *r*-ecgonine esters break down into β-cycloheptatriene-carboxylic acid, as follows :—



Ecgonine possesses the properties of an amino-acid, forming salts with both bases and acids. The presence of the carboxyl group is not shown by any acid reaction, but is revealed in the stability of the alkali

[1] *Ann.*, 1903, **326**, 47. [2] *Ber.*, 1898, **31**, 2655.

salts towards carbon dioxide, and the production of esters on treatment with alcohols and hydrogen chloride. The alcoholic hydroxyl group may be detected by the formation of esters on treatment with acid chlorides and anhydrides, and in the ease with which the compound parts with water and passes into anhydro-ecgonine (ecgonidine).

Preparation of l-*Ecgonine.*—*l*-Ecgonine is obtained by hydrolysing *l*-cocaine with hydrochloric acid, dilute sulphuric acid, or barium hydroxide. Similarly, the uncrystallisable mixture of partly amorphous bases, obtained in quantity as a by-product in the isolation of cocaine from coca leaves, also yields *l*-ecgonine on hydrolysis.

The preparation of ecgonine from cocaine residues is of value in the technical production of cocaine, since ecgonine can readily be converted into cocaine.

l-Ecgonine crystallises in monoclinic hemimorphic prisms (+1 mol. H_2O), which become anhydrous at 120° and melt with decomposition at 198°.

d-**Ecgonine,** (*d*-ψ-ecgonine), was first obtained by Einhorn by warming ordinary *l*-ecgonine with concentrated alkali. It also results from the treatment of cocaine, benzoyl ecgonine, or the alkaloids accompanying cocaine with caustic potash, when the *l*-ecgonine first formed undergoes molecular rearrangement. Liebermann and Giesel obtained it as a fission product of the *d*-cocaine discovered by them among the coca alkaloids. It forms monoclinic prisms or plates of melting-point 264°.

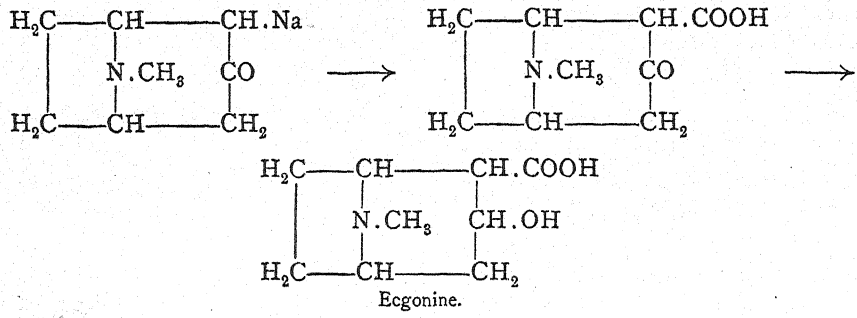
r-**Ecgonine,** the racemic compound, was prepared synthetically by Willstätter [1] in the following manner, thus completing the synthesis of cocaine.

Sodium tropinone, suspended in ether, unites with carbon dioxide at room temperature to give sodium tropinone-carboxylate. This compound can be obtained more readily by the simultaneous action of sodium and carbon dioxide on the amino-ketone. When the crude tropinone-carboxylate is reduced in cold, faintly acid solution with sodium amalgam it yields a mixture of two isomeric compounds, having the composition of ecgonine but of different constitutions, viz., ψ-tropine-O-carboxylic acid and *r*-ecgonine. Only the latter is of interest in this connection, and its formation is probably due to part of the sodium tropinone reacting as the ketonic salt (*cf.* acetoacetic ester) and thus yielding tropinone-β-carboxylic acid, which on reduction passes into *r*-ecgonine, as shown on next page.

A further synthesis of *r*-ecgonine was carried out by Willstätter [2] in connection with the synthesis of tropinone described on p. 725, tropinone-carboxylic ester being converted by reducing agents into the ester of *r*-ecgonine.

r-Ecgonine contains four asymmetric carbon atoms and is not affected by heating with alkalis. It crystallises with 3 mols. H_2O, and melts with decomposition at 251°.

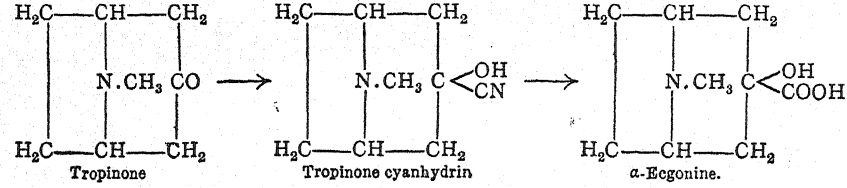
[1] Willstätter and Bode, *Ann.*, 1903, **326**, 47. [2] Willstätter and Bommer, *Ann.*, 1921, **422**, 15.



Ecgonine.

α-Ecgonine, 3-Hydroxytropane-3-Carboxylic Acid

Before the constitution of *l*-ecgonine was known in detail, an attempt had been made to synthesise the racemic compound from tropinone. As a ketone, the latter unites with hydrogen cyanide to form *tropinone cyanhydrin*. This on hydrolysis yields a compound of the composition of ecgonine, from which it differs in having the carboxyl and hydroxyl groups both attached to the same carbon atom. For this structural isomeride of ecgonine Willstätter proposed the name *α*-ecgonine.



Tropinone — Tropinone cyanhydrin — α-Ecgonine.

On benzoylation the methyl ester of *α*-ecgonine is converted into *α*-cocaine (see p. 738). The only interest of these *α*-compounds lies in the part they have played in furthering our knowledge of the constitution of ecgonine. Since *α*-ecgonine was not identical with ordinary ecgonine, it followed that the carboxyl group in the latter could not occupy the *α*-position.

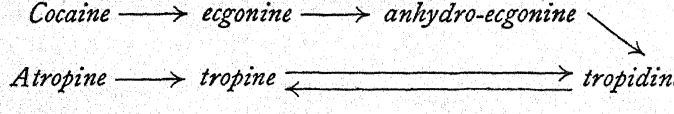
In chemical behaviour *α*-ecgonine and its derivatives differ markedly from ordinary ecgonine. Whereas the methiodides of the ecgonine group, being *β*-betaines, are easily decomposed by alkalis, those of the *α*-ecgonine group, being *γ*-betaines, exhibit great stability.

Tropidine (Tropene)

Tropidine (formula, see p. 720) has been mentioned frequently in the foregoing pages. It was first prepared from tropine by heating it to 180° with fuming hydrochloric acid and glacial acetic acid, or with sulphuric acid (Ladenburg). As Einhorn has shown, it is also formed by heating anhydro-ecgonine (tropene-2-carboxylic acid) with concentrated hydrochloric acid to 280°, when carbon dioxide is eliminated :

$$\underset{\text{Anhydro-ecgonine}}{C_8H_{12}(CO_2H)N} = CO_2 + \underset{\text{Tropidine.}}{C_8H_{13}N}$$

Tropidine is further formed by heating *ψ*-tropine with glacial acetic acid containing hydrochloric or sulphuric acid.



The *syntheses of tropidine* carried out by Willstätter have already been described. These are of great importance, since tropidine may be converted through ψ-tropine into tropine (see pp. 704, 705), and also into *r*-ecgonine. In this manner several alkaloids of the tropane series, particularly atropine, are accessible from the synthetic side.

Properties of Tropidine.—Tropidine is a liquid base with a stupefying odour like that of coniine. It boils at 162° to 163° (corr.) and is less soluble in hot water than in cold. The aqueous solution turns litmus paper blue.

When treated with excess of bromine at 170° to 180°, tropidine yields ethylene dibromide and dibromo-pyridine (Ladenburg, 1883).

On exhaustive methylation tropidine first gives *α-methyltropidine*, and finally, by distillation of α-methyltropidine-methylammonium hydroxide, it yields *tropilidene* or *cycloheptatriene* [1] (see p. 723).

$$C_7H_9.N(CH_3)_3OH = C_7H_8 + N(CH_3)_3 + H_2O$$

Alkaloids of the Tropane Series

To this group belong the alkaloids of the Solanaceæ and the coca alkaloids.

1. ALKALOIDS OF THE SOLANACEÆ

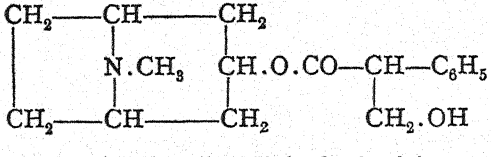
In many members of the Solanum family, such as *Atropa belladonna* (Deadly Nightshade), *Datura stramonium* (Thorn apple), *Hyocyamus niger* (Henbane), are found a number of alkaloids closely related to each other in their properties and chemical constitution. Chief among these are two isomerides of the composition $C_{17}H_{23}NO_3$, viz., optically inactive *atropine* and laevorotatory *hyoscyamine*.

Atropine is actually the racemic modification of hyoscyamine.

Accompanying the above are found the following less completely investigated Solanum bases:

Atropamine	$C_{17}H_{21}NO_2$
Belladonnine	$C_{17}H_{21}NO_2$
Hyoscine or scopolamine	$C_{17}H_{21}NO_4$

Atropine, tropine ester of *dl*-tropic acid



This case occurs in the Deadly Nightshade (*Atropa belladonna*), in *Datura stramonium*, and in the root of *Scopolia japonica*.

According to Mein, 1000 parts of dried belladonna root contain about 3·3 parts of atropine, which is isolated by extraction with alcohol.

Atropine is optically inactive and crystallises from alcohol or chloroform

[1] Merling, *Ber.*, 1891, **24**, 3109. Willstätter, *Ber.*, 1898, **31**, 1534.

in prisms, m.p. 115° to 116°. It has a sharp and bitter taste and is a strong poison. Owing to its property of dilating the pupil of the eye (mydriasis) it is extensively employed in medicine. By its use it is possible to counteract the stoppage of the heart caused by muscarine.

Inactive atropine results from the racemisation of its stereo-isomeride hyoscyamine, (1) when the latter is heated to 110° in absence of air, (2) on being treated in alcoholic solution with a few drops of alkali, or (3) spontaneously in the course of time.

When treated with nitric acid, and also when warmed with acetic or benzoic anhydride, or phosphorus pentoxide, atropine loses a molecule of water and yields *apoatropine*, $C_{17}H_{21}NO_2$, which has been found to be identical with the naturally occurring *atropamine*. The latter crystallises in prisms, m.p. 60° to 62°, and does not induce mydriasis. If atropine is heated to 130°, it loses water in another manner and a certain proportion is converted into *belladonna*, an uncrystallisable mass with the appearance of varnish.

Atropine salts have only a low power of crystallisation. Atropine sulphate, $(C_{17}H_{23}NO_3)_2H_2SO_4+H_2O$, which is employed in eye surgery, is obtained in crystalline condition by dropping sulphuric acid dissolved in absolute alcohol (1 : 10) into atropine (10 parts) in dry ethereal solution. The sulphate separates in the form of needles.

Constitution and Synthesis of Atropine

In 1863 Kraut discovered that atropine, on being boiled with aqueous baryta, decomposed to yield *tropine* and *atropic acid.*

A year later it was shown by Lossen that the primary product of decomposition was not atropic acid, $C_9H_8O_2$, but *tropic acid*, $C_9H_{10}O_3$, and that the latter was then converted into the former by loss of 1 mol. water. Consequently the change undergone by atropine is merely the hydrolysis of an ester into acid and (basic) alcohol.

$$\underset{\text{Atropine}}{C_{17}H_{23}NO_3} + H_2O = \underset{\text{Tropine}}{C_8H_{15}NO} + \underset{\text{Tropic acid.}}{C_9H_{10}O_3}$$

By reversing the above process Ladenburg,[1] in 1879, effected a partial synthesis of atropine. On treating tropine tropate with hydrochloric acid he succeeded in regenerating atropine, thus proving it to be the tropine ester of tropic acid.

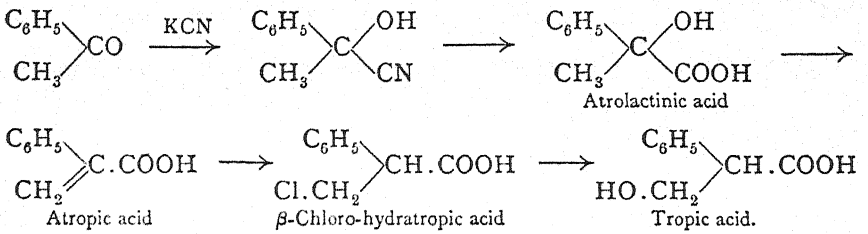
The problem of the constitution of atropine therefore resolved itself into two parts : the study of tropic acid and that of tropine.

The structure of tropic acid was soon cleared up and the compound synthesised by Ladenburg and Rügheimer.[2] It is, however, more readily prepared by the synthesis of E. Müller, in which phenylacetic ester, $C_6H_5.CH_2.COOC_2H_5$, is condensed with formic acid to give *formyl-*

[1] *Ber.*, 1879, **12**, 941 ; **13**, 104. *Ann.*, 1883, **217**, 78. Wolffenstein and Mamlock, *Ber.*, 1908, **41**, 723. [2] *Ber.*, 1880, **13**, 373 Spiegel, *Ber.*, 1881, **14**, 236. Kraut and Merling, *Ber.*, 1881, **14**, 330. *Ann.*, 1881, **209**, 3.

phenylacetic ester. This on reduction with aluminium amalgam yields *tropic ester*.[1]

Another method of preparing this important acid is that due to McKenzie and Wood.[2] Acetophenone is converted into atrolactinic acid, which on being heated under diminished pressure gives atropic acid. The latter unites with HCl in ethereal solution to form β-chlorohydratropic acid, which finally yields tropic acid on being boiled with aqueous sodium carbonate.



The presence of an asymmetric carbon atom in tropic acid indicated the possibility of resolving the acid into its active components and thus of preparing optically active atropines. The resolution of tropic acid was effected by Ladenburg by means of the quinine salt, and from the active components the *active atropines* were then built up. By using other acids in place of tropic acid Ladenburg prepared other esters of tropine, to which he gave the collective name of *tropeïnes*. These artificial alkaloids are described below.

It was not until much later that the structure of the alcohol tropine, the remaining hydrolysis product of atropine, was successfully elucidated and its synthesis accomplished. This has been described in detail on pp. 722 *et seq*.

Hence the complete **synthesis of atropine** involves the following stages :—1. Synthesis of glycerol. 2. Glycerol into glutaric acid. 3. Glutaric acid into suberone. 4. Suberone into tropidine. 5. Tropidine into tropine. 6. Synthesis of tropic acid. 7. Atropine from tropine and tropic acid.

For the *relationship between atropine and cocaine* see pp. 722 to 733.

Homatropine or *phenyl-glycolyl-tropeïne*, $C_{16}H_{21}NO_3$, is by virtue of its physiological action the most important compound of the tropeïne group after atropine and hyoscyamine. It is prepared from tropine and mandelic acid, and crystallises from absolute ether in transparent prisms, which are deliquescent and melt at 95·5° to 98·5°. *Homatropine hydrobromide*, $C_{16}H_{21}NO_3,HBr$, crystallises in rhombic plates and is only moderately soluble in cold water.

[1] E. Müller, *Ber.*, 1918, 51, 252. W. Wislicenus and Bilhuber, *ibid.*, 1237. [2] McKenzie and Wood, *J. C. S.*, 1919, 115, 830.

In the form of its hydrobromide, homatropine possesses almost as powerful an action in dilating the pupil of the eye as atropine, but the effect disappears comparatively rapidly. It behaves similarly with respect to the paralysis of the power of accommodation. Homatropine is a much weaker poison than atropine and is also used in eye surgery.[1]

According to the investigations of Ladenburg and Völkers the mydriatic power of the tropeïnes is not solely dependent on the presence of the tropine residue in the molecule; it is also necessary for the latter to be united to an acid containing an alcoholic hydroxyl grouping.[2] Some exceptions to this statement are known.

Hyoscyamine, l-*Tropic Ester of Tropine*

Hyoscyamine was first prepared from henbane, and occurs also in a number of other plants. It has been found by Dunstan and Brown [3] in *Hyoscyamus muticus*, and by Thoms and Wentzel [4] in mandragora root.

It crystallises from alcohol in needles, m.p. 108·5°, and resembles atropine in its sharp, penetrating taste and mydriatic action. The main difference between these two alkaloids lies in the laevorotation of hyoscyamine as compared with the optical inactivity of atropine.

The conversion of hyoscyamine into atropine (racemisation) may be effected by fusion, or by the addition of a small amount of alkali to an alcoholic solution of the compound. It has also been found that the change takes place slowly, without appreciable hydrolysis, when hyoscyamine is allowed to stand in alcoholic solution,[5] and is accelerated by the addition of tropine. Since hyoscyamine undergoes hydrolysis in aqueous solution, even at the ordinary temperature, to form *l*-tropic acid and inactive tropine, it follows that the conversion of hyoscyamine into atropine is due to alteration of the tropic acid component. This change is now known to be due to racemisation, the racemic nature of the inactive tropic acid from atropine having been established by resolution.

Additional proof that the isomerism of atropine and hyoscyamine depends solely on the inactivity or activity of the tropic acid residue has been supplied by the conversion of atropine into *d*- and *l*-hyoscyamines. This was first effected by hydrolysing commercial atropine into tropine and tropic acid, resolving the latter, and uniting the *d*- and *l*-tropic acids separately with tropine to give *d*- and *l*-hyoscyamines.[6] Barrowcliff and Tutin [7] also resolved atropine directly, by use of *d*-camphor-sulphonic acid.

Hyoscyamine can therefore be synthesised by stages similar to those used in the case of atropine (p. 735), the final combination being with *l*-tropic acid in place of the racemic compound. Natural *l*-rotatory hyoscyamine has about a hundred times greater physiological activity than the *d*-form.

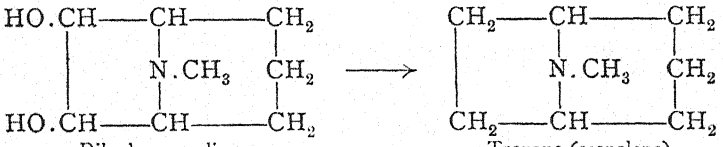
Dehydrating agents convert hyoscyamine into *atropamine* and *belladonnine*. These alkaloids are also obtained in the same way from atropine (see p. 734).

The optically isomeric alkaloids **hyoscine** and **scopolamine**, $C_{17}H_{21}NO_4$, are also found in plants of the Solanaceæ family. Scopolamine (m.p. of monohydrate, 59°) is laevorotatory, and with alkalis is readily racemised to hyoscine. On hydrolysis scopolamine yields tropic acid and *scopoline*, but it is not the scopoline ester of tropic acid. Recent

[1] Ladenburg, *Ann.*, 1883, **217**, 82. Jowett and Pyman, *J. C. S.*, 1909, **95**, 1090. [2] Compare also J. v. Braun, O. Braunsdorff and K. Räth, *Ber.*, 1922, **55**, 1666. [3] *J. C. S.*, 1899, **75**, 72. [4] *Ber.*, 1898, **31**, 2031 [5] Gadamer, *J. C. S.*, 1901, **80**, A, i, 605. [6] Amenomiya, *J. C. S.*, 1903, **84**, A, i, 109. [7] Barrowcliff and Tutin, *J. C. S.*, 1909, **95**, 1966.

work by Hess and Wahl [1] points to the alkaloid being the tropic ester of a symmetrical base which is isomeric with scopoline, and into which it isomerises during the process of hydrolysis.

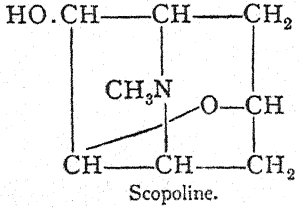
Scopoline, $C_8H_{13}NO_2$, strongly resembles tropine, $C_8H_{15}NO$, in its properties. With HBr in glacial acetic acid it gives an addition compound which is readily reduced to dihydro-scopoline. The latter, when heated with concentrated hydriodic acid, is reduced further to tropane.[2] This reaction establishes the constitution of the carbon framework of scopoline, and the close relationship of the compound to tropine.



Dihydro-scopoline — Tropane (scopolane).

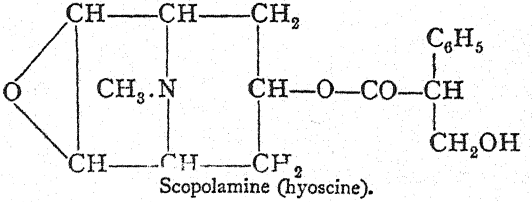
Scopoline has also been submitted to exhaustive methylation,[3] with results which confirm the constitution (formula I) suggested for it by King.[4] Scopolamine is then represented by formula II.

I.



Scopoline.

II.



Scopolamine (hyoscine).

The physiological action of hyoscine and scopolamine is sedative, without the deleterious secondary effects of atropine. In mydriatic action the alkaloid is many times more powerful than atropine. Scopolamine is preferable to hyoscine and is largely used as a mydriatic and sedative.

2. THE COCA ALKALOIDS

The leaves of *Erythroxylon coca* contain a large number of alkaloids. In addition to the hygrines, already described on pp. 716 *et seq.*, there are present the following :—

Cocaine	$C_{17}H_{21}NO_4$
Cinnamyl-cocaine	$C_{19}H_{23}NO_4$
α-Truxilline	$(C_{19}H_{23}NO_4)_2$
β-Truxilline	$(C_{19}H_{23}NO_4)_2$
Benzoyl-ecgonine	$C_{16}H_{19}NO_4$
Tropacocaine	$C_{15}H_{19}NO_2$

All these compounds are tropane derivatives and therefore contain a pyrrolidine nucleus. With the exception of tropacocaine they all yield

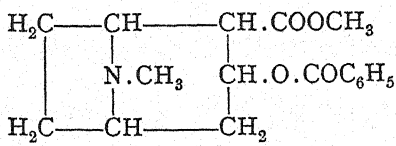
[1] K. Hess and Wahl, *Ber.*, 1922, 55, 1979. Willstätter and Berner, *Ber.*, 1923, 56, 1079. [2] K. Hess and co-workers, *Ber.*, 1915, 48, 2057 ; 1918, 51, 1007. [3] Hess, *Ber.*, 1919, 52, 1947. Gadamer and Hammer, *J. C. S.*, 1921, 120, A, i, 588. [4] King, *J. C. S.*, 1919, 115, 486.

ecgonine as the basic product of decomposition, and stand in close relationship to the Solanaceæ alkaloids.[1]

Before reading the following description of the coca alkaloids, reference should be made to the preceding pages (729 *et seq.*) dealing with ecgonine.

Among all the coca alkaloids only *l*-cocaine is of therapeutic value, the others being without particular physiological action. These inactive alkaloids, however, can be utilised for the production of *l*-ecgonine (Liebermann).

Cocaine, *methyl ester of benzoyl-ecgonine.*



Corresponding to the different stereoisomeric ecgonines (see p. 729), three stereoisomeric cocaines are known, namely *l*-cocaine, *d*-cocaine (*d*-ψ-cocaine) and *r*-cocaine; to these must be added the structurally isomeric *α*-cocaine derived from *α*-ecgonine (see p. 732).

Of these alkaloids *l*-cocaine is the most valuable and most important. It is highly prized as a local anæsthetic and, owing to the short length of time during which its effect is operative, is largely used in eye surgery and dentistry.[2] It is employed in the form of its hydrochloride and cannot be used for producing prolonged anæsthesia, on account of its poisonous properties.

Occurrence, Disruption Products and Preparation of *l*-Cocaine

l-Cocaine was first isolated by Niemann in 1860 from Peruvian coca leaves (*Erythroxylon coca*). It crystallises in prisms, melting at 98°, and is usually obtained from the above source by extraction with high-boiling petroleum.

On being boiled with water it is hydrolysed to methyl alcohol and benzoyl-ecgonine.

$$\underset{\text{Cocaine}}{C_{17}H_{21}NO_4}+H_2O = \underset{\text{Benzoyl-ecgonine.}}{C_{16}H_{19}NO_4}+CH_3OH$$

More powerful hydrolysis by means of mineral acids, baryta-water, or caustic alkali results in the benzoyl-ecgonine undergoing further decomposition into *l*-ecgonine and benzoic acid.

$$\underset{\text{Cocaine}}{C_{17}H_{21}NO_4}+2H_2O = \underset{\text{Ecgonine}}{C_9H_{15}NO_3} + \underset{\text{Benzoic acid}}{C_7H_6O_2} + \underset{\text{Methyl alcohol.}}{CH_3OH}$$

These reactions led to the conclusion that cocaine is the methyl ester of benzoyl-ecgonine, and prepared the way for its preparation from ecgonine.

[1] Compare the conversion of cocaine into atropine, pp. 729 and 732. [2] For the work of A. Einhorn dealing with the relation between the constitution and physiological action of organic compounds see *Ann.*, 1900, 311, 26, 154.

A partial synthesis of *l*-cocaine on these lines was first effected by Merck, by heating *l*-ecgonine with benzoic anhydride and methyl iodide.

$$C_8H_{13}N\begin{cases}COOH\\OH\end{cases} + (C_6H_5CO)_2O + CH_3I$$

Ecgonine

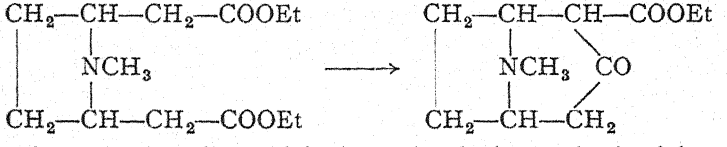
$$= C_8H_{13}N\begin{cases}COOCH_3\\O.COC_6H_5\end{cases} + HI + C_6H_5.COOH$$

Cocaine.

The conversion of ecgonine into cocaine may also be brought about by other methods of esterification. According to Liebermann,[1] cocaine is obtained in good yield when *l*-ecgonine is treated in concentrated aqueous solution with benzoic anhydride, and the benzoyl-*l*-ecgonine so obtained is esterified with methyl alcohol in the presence of hydrochloric or sulphuric acid.[2] Since considerable amounts of *l*-ecgonine can be prepared from the therapeutically valueless alkaloids found with natural cocaine (*cf.* p. 731), the above method of increasing the supply of *l*-cocaine is of special importance.

Synthetic Cocaines and their Resolution

Pseudococaine, the racemic form of the *d*-pseudococaine which is present in small amount in the coca-plant, has been synthesised by Willstätter, the first stage being the intramolecular condensation of N-methyl-pyrrolidine-diacetic ester. This reaction resembles an *internal* acetoacetic ester condensation, and leads to the formation of tropinone carboxylic ester.



Tropinone carboxylic acid had previously been obtained by treating sodio-tropinone with carbon dioxide (see p. 731) and without being isolated was reduced to *r*-ecgonine. By the above condensation the ester may be prepared directly. The same ester was also obtained using a modification of Robinson's method. Willstätter found that when succindialdehyde is allowed to react with methylamine and the monoester of acetone dicarboxylic acid (p. 726), carbon dioxide may be detached from the free carboxyl group in the resulting compound to give the ester of tropinone carboxylic acid.

Two Racemic Ecgonines.—Methyl tropinone carboxylate, on being reduced with sodium amalgam in weak acid solution, gave a mixture from which the methyl esters of *r*-pseudoecgonine and *r*-ecgonine were isolated. The former bears the same relationship to natural *d*-cocaine

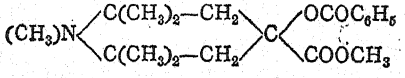
[1] *Ber.*, 1888, **21**, 3196; 1894, **27**, 2051. [2] Other esters of benzoyl-*l*-ecgonine are obtained by use of the corresponding alcohols. These produce the same physiological effects as *l*-cocaine, over which they have no special advantage.

(*d*-pseudococaine) as the latter does to ordinary *l*-cocaine. Pseudotropine is also formed as a by-product in the above reduction, owing to loss of carbon dioxide from the carboxyl group.

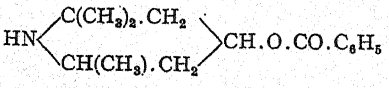
Resolution of the Racemate.—The benzoyl derivative of the second racemic ester, which is the more important owing to its closer connection with ordinary cocaine, was resolved by the recrystallisation of its di-*d*-tartrate. After removing tartaric acid, the less soluble salt of the *l*-base gave an ester identical with ordinary cocaine. Among the various cocaines two *d*-, two *l*- and the two *r*-isomerides have now been prepared in the pure state.[1]

Psicaine.[2]—As already stated, two racemic alkaloids were prepared during the cocaine syntheses, one of which corresponds to natural *l*-cocaine. The other, *r*-pseudococaine (*ψ*-cocaine), m.p. 81·5°, was subsequently converted into the corresponding ecgonine (by removal of the benzoyl group) and the latter resolved by means of bromo-camphorsulphonic acid. The *d*-pseudococaine obtained by benzoylation of the *d*-pseudoecgonine ester was found to possess the most powerful anæsthetic action, coupled with relatively low toxicity. Its tartrate, $C_{17}H_{21}O_4N,C_4H_6O_6$, is known as psicaine, and forms a microcrystalline powder, $[\alpha]_D^{20} + 43°$ (in 5 per cent. aqueous solution).

Eucaine is obtained from triacetonamine, and is a substitute for cocaine. The similar anæsthetic action of these two substances may be explained by their similarity in structure. Eucaine is a piperidine derivative of the formula

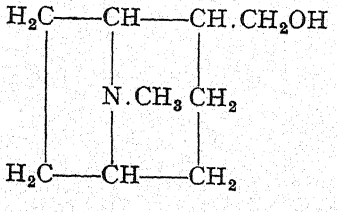


β-Eucaine is a more satisfactory cocaine substitute of the following structure:

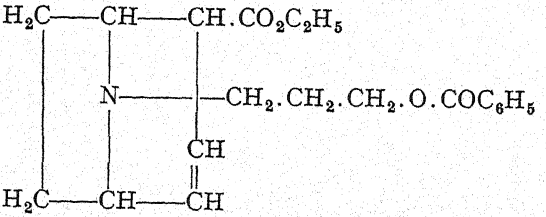


Homotropeines and Eccaine from Cocaine[3]

Starting from ecgonidine (anhydro-ecgonine), which is easily obtained from cocaine, J. v. Braun prepared in succession ecgonidine ethyl ester, hydro-ecgonidine ethyl ester, and finally, by reducing the carbethoxy group, obtained the amino-alcohol I, *homotropine* (m.p. 85°).



I.



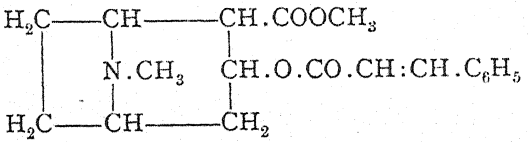
II.

[1] R. Willstätter, Pfannenstiehl and Bommer, *Ann.*, 422, 1, 15. [2] R. Willstätter, *Münch. Med. Wochenschr.*, 1924, 71, 849. R. Willstätter and Gottlieb, *Ann.*, 1923, 434, 111. [3] J. v. Braun and Müller, *Ber.*, 1918, 51, 235.

Like tropine, this compound contains a hydroxyl group in the γ-position to nitrogen, and can be esterified with various acids, including tropic acid. Physiological investigation showed that the acidyl derivatives of homotropine—known as *homotropeines*—possess the same properties as the tropeines, and that homotropine tropate, **mydriasine,** is a mydriatic of the strength of atropine.

Eccaine (formula II) is obtained from cocaine in the following stages. Cocaine is demethylated to cyano-norcocaine, and the latter hydrolysed to norecgonidine and esterified. The secondary nitrogen atom in norecgonidine ethyl ester is then linked up with a γ-benzoyl-oxypropyl group. Eccaine is not only a stronger anæsthetic than cocaine but is also non-toxic, and can readily be sterilised in aqueous solution. Consequently it is an anæsthetic of valuable properties.[1] It is an oil and gives a hydrochloride of melting-point 117°.

Cinnamyl-cocaine, *methyl ester of cinnamyl-ecgonine.*



l-*Cinnamyl-cocaine* is found in practically all varieties of coca, particularly in that of Java. It was investigated by Liebermann,[2] and prepared from *l*-ecgonine by the action of cinnamic anhydride and subsequent esterification of the cinnamyl derivative with methyl alcohol and hydrochloric acid. It crystallises from hot benzene-ligroin solution in needles of melting-point 121°.

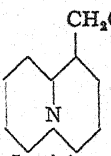
Alkaloids of the Lupin Group

The following alkaloids contained in the various lupin families were originally investigated by E. Schmidt.[3]

Lupinine, $C_{10}H_{19}ON$, in *Lupinus luteus* and *L. niger*.

Sparteïne, $C_{15}H_{26}N_2$, in *L. luteus* and *L. niger*.

Lupanine, $C_{15}H_{24}ON_2$, occurs in the racemic and laevo forms in *Lupinus albus*, *Lupinus angustifolius* and *Lupinus perennis*.



Lupinine.

The structure of lupinine has been established by degradations carried out by Willstätter and Karrer and by the synthesis of the racemic compound by Clemo. In the annexed formula the rings are fully saturated.

The simultaneous occurrence of sparteïne and lupinine in yellow lupins points to the probability of a constitutional relationship between these two alkaloids.[4]

IV. ALKALOIDS OF THE QUINOLINE GROUP

In this section are included the important Cinchona bases, quinine and cinchonine, together with the Strychnos bases, strychnine and brucine.

Quinine and Cinchonine

Cinchona or Peruvian bark, which has been used in Europe since the middle of the seventeenth century in the treatment of fevers is obtained

[1] See J. v. Braun and Müller, *Ber.*, 1918, **51**, 235. [2] *Ber.*, 1888, **21**, 3373. [3] E. Schmidt, *J. C. S.*, 1897, **72**, A, i, 645. See also *J. C. S. Ann. Rep.*, 1928, 194. [4] Willstätter and Marx, *Ber.*, 1904, **37**, 2351.

from various trees of the Cinchona family found mainly in Bolivia and Peru. It contains, in addition to a tannin and quinic acid, a series of alkaloids which are closely related to one another in structure. The most important of these are *quinine*, $C_{20}H_{24}N_2O_2$, to which the curative action of the bark is chiefly due, and *cinchonine*, $C_{19}H_{22}N_2O$.

Quinine generally crystallises with 3 mols. H_2O, and in the anhydrous condition melts at 177°; it separates from alcohol and ether in shining needles. It is present in yellow calisaya bark to the extent of 2 to 3 per cent., has an alkaline reaction, a bitter taste, and as a diacid base forms neutral and acid salts. Quinine is one of the most valuable medicines, especially in the treatment of intermittent fevers such as malaria and swamp fever, and is an antidote against many infections caused by micro-organisms.

Cinchonine accompanies quinine and is found in particularly large amounts in grey cinchona bark (*Cinchona Huanaco*), in which it occurs up to 2·5 per cent. It crystallises from alcohol in white prisms, sublimes readily and melts at 255°. As a febrifuge it is less active than quinine.

Quinine and cinchonine are similarly constituted, and therefore the results obtained by the investigation of these compounds have often supplemented one another. In many cases information gained with regard to cinchonine has been applied without modification to quinine.

Both alkaloids were discovered in the year 1820 by Pelletier and Caventou, and their constitutional formulæ have been deduced from evidence gradually accumulated from a large number of investigations.

As already stated, the composition of cinchonine is $C_{19}H_{22}N_2O$, and that of anhydrous quinine, as determined by Liebig, is $C_{20}H_{24}N_2O_2$. In their empirical formulæ, therefore, these two bases differ in that quinine contains one atom of carbon, one atom of oxygen and two atoms of hydrogen more than cinchonine.

The molecules of cinchonine and quinine possess two tertiary nitrogen atoms.[1] *One oxygen atom in quinine is contained in a hydroxyl and the other in a methoxyl group.*

The presence of a hydroxyl group in quinine is indicated by several reactions. For example, quinine forms a monobenzoyl derivative (Schützenberger), a mono-acetyl derivative (Hesse), and a silver salt of the composition $C_{20}H_{23}AgN_2O_2$ (Skraup).

The existence of a methoxyl group is shown by the formation of methyl chloride (accompanied by intramolecular rearrangement) when quinine is heated with concentrated hydrochloric acid. In this case the other primary reaction product is *apoquinine*, which in turn gives a diacetyl derivative and therefore contains two hydroxyl groups.

$C_{19}H_{20}N_2(OH)(OCH_3)$	$C_{19}H_{20}N_2(OH)_2$
Quinine	Apoquinine.

Proof that the oxygen atom of cinchonine is also present in a hydroxyl

[1] Skraup and Koneck, *Ber.*, 1893, **26**, 1968.

group is supplied by reactions similar to those quoted above for quinine, *e.g.* by the formation of acyl derivatives.

Information as to the position of the hydroxyl group and the general structure of the cinchona alkaloids has been gained largely by the decompositions of these compounds carried out by Skraup, Königs and v. Miller.

Decomposition of Quinine and Cinchonine by Fusion with Potash and by Oxidation

Fusion of these alkaloids with potash led to the conclusion that cinchonine contains a quinoline or lepidine group, and that quinine is derived from 6-methoxy-lepidine. This is in complete agreement with the results obtained by the oxidation of the alkaloids.

When oxidised with a solution of chromic acid in sulphuric acid solution, cinchonine and quinine break up, on the one hand, into the 4-carboxylic acids of quinoline and of 6-methoxy-quinoline (known respectively as cinchoninic acid and quininic acid), and on the other, into derivatives of pyridine. Hence the molecule of the cinchona alkaloids must contain these two ring systems linked together.

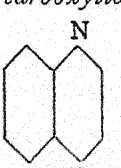
The carboxylic acids of quinoline were soon identified as such, thus establishing the presence of a quinoline nucleus (" quinoline half ") in the alkaloids.

On the other hand, the investigation of the pyridine derivatives (cincholoipon, meroquinene, cincholoiponic acid and loiponic acid) proved to be exceedingly difficult, and has only recently been brought to a successful issue. For a long time nothing was known of the constitution of that part of the molecule giving rise to the pyridine compounds, and it was described briefly by Skraup [1] as the " second half " of the cinchona alkaloids. From the following it will be seen that this term is used for the grouping $(C_{10}H_{16}NO)$—, which in cinchonine is combined with the quinoline residue (C_9H_6N)—, and in quinine with 6-methoxy-quinoline residue $(CH_3O.C_9H_5N)$—.

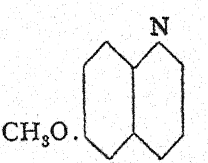
Constitution of the " Quinoline Half " of Quinine and Cinchonine

The key to the constitution of the " quinoline half " lies in the following facts :

1. When cinchonine is subjected to energetic oxidation, about 50 per cent. of the product consists of *cinchoninic acid*, which is identical with *quinoline-4-carboxylic acid*.



Cinchoninic acid,
Quinoline-4-carboxylic acid.



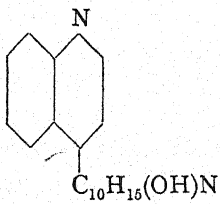
Quininic acid,
6-Methoxy-cinchoninic acid.

[1] Skraup, *Monats.*, 1888, **9**, 783.

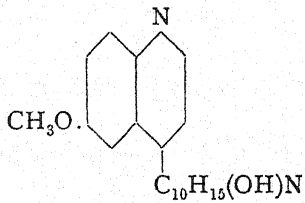
From this it follows that cinchonine is a derivative of quinoline, containing a side chain in the 4-position. The hydroxyl group of cinchonine is also present in the side chain because, had it been situated in the quinoline nucleus, the oxidation product would have been a hydroxy-cinchoninic acid.

The composition of this side chain must be $C_{10}H_{15}(OH)N$, *i.e.*, the difference between the formula for cinchonine, $C_{19}H_{21}(OH)N_2$, and that of the quinoline radical, C_9H_6N. Hence the structure of cinchonine may be represented provisionally by formula I.

I.



II.



2. When quinine is energetically oxidised with chromic acid [1] it gives an acid, $C_{11}H_9NO_3$, known as quininic acid. The difference between this compound and cinchoninic acid, $C_{10}H_7NO_2$, is the same as that between quinine and cinchonine.

Quininic acid was shown by Skraup to be 6-methoxy-cinchoninic acid (see p. 696). From this it was concluded that quinine is a methoxy-cinchonine, and that the methoxyl group replaces the hydrogen atom corresponding to position 6 of the quinoline nucleus present in cinchonine. Quinine was therefore represented by formula II.

In the above oxidations the disruption of the "second half" of cinchonine and quinine yields in each case the same derivatives of pyridine. The "second half" of cinchonine must therefore be the same as the "second half" of quinine, and the difference in the two alkaloids may be summarised in the statement that the former is a derivative of quinoline and the latter of 6-methoxy-quinoline.[2]

Information as to the structure of the cinchona bases has also been obtained by the investigation of certain intermediate products of oxidation, known as "tenines."

Skraup found that the formation of *cinchotenine* by the oxidation of cinchonine with potassium permanganate is accompanied by the production of formic acid, according to the equation

$$\underset{\text{Cinchonine}}{C_{19}H_{22}N_2O}+4O=\underset{\text{Cinchotenine}}{C_{18}H_{20}N_2O_3}+\underset{\text{Formic acid.}}{H.COOH}$$

[1] Skraup, *Monats.*, 1881, **2**, 591; 1883, 4, 695. *Ber.*, 1879, **12**, 1106; 1883, **16**, 2684.

[2] Demethylated quinine—*i.e.*, the derivative of 6-hydroxy-quinoline corresponding to quinine—is found in a bark obtained from *Remija pedunculata*. It is known as **cupreine**, and on methylation is converted into quinine. Thus quinine is the methyl ether of cupreine, to which it is related as anisole to phenol, and, as will be seen later, as codeine is to morphine. The higher homologues of hydro-cupreine have a strong disinfectant action towards pathogenic bacteria. **Eucupine**, the hydrochloride of iso-*amyl-hydro-cupreine*, and **vuzine**, or iso-*octyl-hydro-cupreine*, are commercial products. Eucupine also possesses an anæsthetic action. Klapp, *C.*, 1919, **I**, 122. Morgenroth, *Ber.*, *Deut.-pharm. Ges.*, 1919, **29**, 233.

Similarly quinine, when oxidised with potassium permanganate, gives formic acid and the corresponding compound *quitenine*.

$$C_{20}H_{24}N_2O_2+4O = C_{19}H_{22}N_2O_4+H.COOH$$

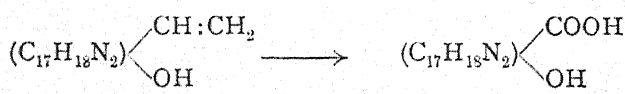
The relationship between cinchonine and cinchotenine is established as follows. When cinchotenine is oxidised with chromic acid it gives cinchoninic acid. The tenine must therefore have been formed from cinchonine by alterations in the *second half* of the molecule. Further, the hydroxyl group of cinchonine is still present as such in cinchotenine, although the acid properties of the latter are due to the additional presence of a carboxyl group.

Since in any case cinchonine only possesses one oxygen atom, and this is contained in a hydroxyl group which is found unchanged in cinchotenine, it follows that the carboxyl must have originated in the oxidation of a group consisting solely of carbon and hydrogen.

Some information about this group is given by the following facts.[1]

Whereas cinchonine has the power of combining directly with hydrogen halide, cinchotenine has not. The formation of the carboxyl group has therefore been accompanied by the disappearance of a group with unsaturated properties. During the destruction of this group only one carboxyl group is formed, and a carbon atom is detached as formic acid. Further, cinchotenine is easily transformed into cincholoiponic acid, which must be regarded as a closed ring compound. Hence the unsaturated group must be present as a side chain. All these facts can only be satisfactorily explained by assuming that cinchonine contains a *vinyl group*. This group unites with hydrogen halides, and on oxidation is ruptured at the double bond with the production of a carboxyl group and formic acid.

$$R.CH:CH_2+4O = R.COOH+H.COOH$$



Cinchonine — Cinchotenine.

The conclusions just arrived at for cinchonine can also be applied directly to quinine, which in an analogous manner may be converted into quitenine.

The property possessed by quinine and cinchonine of uniting with two atoms of bromine, or a molecule of halogen halide, is in complete agreement with the above constitution.

Constitution of the "Second Half" of Quinine and Cinchonine

Valuable information concerning the constitution of the "second half" of the cinchona bases has been obtained by Königs,[2] who examined the hydrolysis products of cinchene and quinene.

[1] Skraup, *Monats.*, 1897, 16, 162. [2] Königs and Comstock, *Ber.*, 1884, 17, 1984; 18, 1219.

Cinchene, $C_{19}H_{20}N_2$, is the anhydro-compound of cinchonine, $C_{19}H_{22}N_2O$, and *quinene*, $C_{19}H_{19}(OCH_3)N_2$, is the anhydro-compound of quinine, $C_{19}H_{21}(OCH_3)N_2O$.

In many respects, these compounds are much more reactive than the parent alkaloids, from which they are obtained by successive treatment with phosphorus pentachloride and alcoholic potash.

Hydrolytic Decomposition of Cinchene and Quinene [1]

According to experimental conditions, cinchene and quinene may take up the elements of water and decompose in two distinct ways.

1. When the anhydro-bases are boiled for a long time with concentrated hydrobromic acid, they take up *one* molecule of water and at the

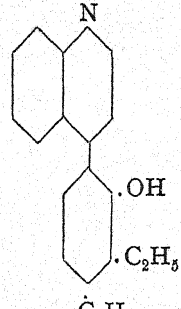
$$\underset{\text{Cinchene}}{C_{19}H_{20}N_2} + H_2O = \underset{\text{Apocinchene.}}{C_{19}H_{19}NO} + NH_3$$

$$\underset{\text{Quinene}}{C_{19}H_{19}(OCH_3)N_2} + H_2O + HBr = \underset{\text{Apoquinene.}}{C_{19}H_{19}NO_2} + NH_3 + CH_3Br$$

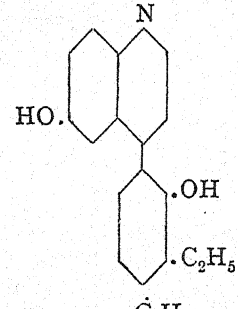
same time lose a molecule of ammonia. In this manner they yield derivatives of 4-phenyl-quinoline, which were described by Königs and Comstock as *apocinchene* and *apoquinene* respectively.

The information gained from the investigation of apocinchene can be directly applied to the constitution of apoquinene, since the latter is easily converted into the former. Thus when apoquinene is heated at 250° with a mixture of ammonium chloride and the double compound of ammonia with zinc chloride, only the hydroxyl group present in the quinoline residue is replaced by an amino group. The amino-apoquinene so obtained can then be converted through the diazo-compound into apocinchene.

Königs showed that apocinchene and apoquinene were derivatives of 4-*o*-hydroxyphenyl-quinoline. They have the following constitutions :



Apocinchene



Apoquinene.

The conversion of apoquinene into apocinchene outlined above leads to the conclusion that apoquinene is hydroxy-apocinchene, and when taken in conjunction with the facts given on p. 744, proves that the addi-

[1] See *Ber.*, 1892, 25, 1541 ; 1894, 27, 900.

tional hydroxyl group must occupy position 6 in the quinoline nucleus. The complete analogy in the behaviour of quinene and cinchene points to the analogous structure of the two anhydro-bases. Hence it may be assumed that quinene is derived from cinchene by replacement of the hydrogen atom in position 6 in the quinoline nucleus by a methoxyl group.

2. When cinchene is heated with 20 per cent. aqueous phosphoric acid at 170° to 180°, it yields *lepidine* and a compound of the composition $C_9H_{15}NO_2$, described by Königs as *meroquinene*. The hydrolysis of cinchene under these conditions therefore takes place according to the equation

$$\underset{\text{Cinchene}}{C_{19}H_{20}N_2} + 2H_2O = \underset{}{C_{10}H_9N} + \underset{\text{Meroquinene.}}{C_9H_{15}NO_2}$$

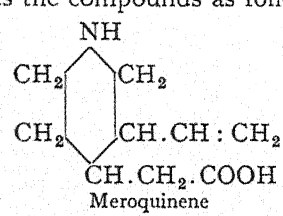
In a similar manner quinene is hydrolysed to 6-methoxy-lepidine and meroquinene.

Constitution of Meroquinene, Cincholoiponic Acid and Loiponic Acid [1]

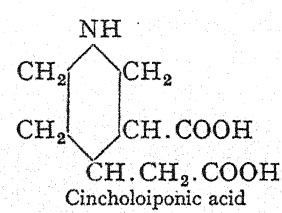
Königs found that meroquinene could be obtained by the direct oxidation of cinchonine with chromic acid, as well as by the hydrolysis of cinchene and quinene. On further treatment with an ice-cold aqueous solution of potassium permanganate and sulphuric acid, meroquinene yields *cincholoiponic acid*. This compound was also obtained by Skraup by the direct oxidation of cinchonine and quinine.

$$\underset{\text{Meroquinene}}{C_9H_{15}NO_2} + 4O = \underset{\text{Cincholoiponic acid}}{C_8H_{13}NO_4} + \underset{\text{Formic acid.}}{H.COOH}$$

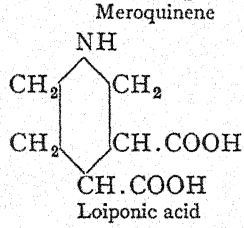
From cincholoiponic acid, by careful oxidation with potassium permanganate, Skraup isolated very small quantities of *loiponic acid*. Hence meroquinene, cincholoiponic acid and loiponic acid represent successive stages in the oxidation of the "second half" of cinchonine. Königs formulates the compounds as follows :—



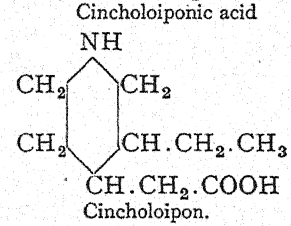
Meroquinene



Cincholoiponic acid



Loiponic acid



Cincholoipon.

On reduction with zinc dust and hydriodic acid, meroquinene is converted into *cincholoipon*, the formula for which is also given above. The presence

[1] Königs, *Ber.*, 1894, **27**, 904, 1501 ; 1895, **28**, 1986, 3150 ; 1897, **30**, 1326, 1332 ; *Ann.*, 1906, **347**, 143. Skraup, *Ber.*, 1895, **28**, 15. *Monats.*, 1896, **17**, 365.

of the carboxyl groups in these products has been proved by the preparation of esters, and that of the imino group by the preparation and properties of nitrosamines, and of acetyl and N-alkyl derivatives.[1] The positions of the carboxyl groups in meroquinene and cincholoipon were finally established as a result of the synthesis of *ethyl quinuclidine*, which is described on p. 749.

The assumption that these compounds contained a pyridine nucleus was based primarily on the formation of *4-methyl-2-ethyl-pyridine* when meroquinene is heated with a solution of mercuric chloride in hydrochloric acid, and also on the conversion of cincholoiponic acid into 4-methylpyridine by means of concentrated sulphuric acid.[2]

The most convincing proof of the presence of a pyridine nucleus in loiponic acid is due to Königs. When this compound is heated with potassium hydroxide it is transformed into an isomeric acid, which is identical with synthetic *hexahydro-cinchomeronic acid* (piperidine-3 : 4-dicarboxylic acid). Loiponic acid is therefore a labile form of hexahydrocinchomeronic acid, which passes into the stable form on being heated with alkali.

The formula for cincholoiponic acid was eventually confirmed by Wohl,[3] who succeeded in synthesising both of the theoretically possible racemic compounds from β-chloro-propionacetal. These racemic compounds were resolved into the four optically active forms, one of which proved to be identical in all respects with the cincholoiponic acid obtained from quinine by Skraup.

The additional knowledge of the constitution of cinchonine and quinine gained by the study of meroquinene, cincholoipon, cincholoiponic acid and loiponic acid may therefore be summarised as follows :—

Of the ten carbon atoms present in the "second half" of the cinchona bases, five are contained in a piperidine nucleus, two in a vinyl group and one in a methyl group. The points at which the vinyl and methyl groups are attached to the piperidine nucleus have been determined.

The hydrolysis of cinchene and quinene to give meroquinene on the one hand, and lepidine or methoxy-lepidine on the other, indicates that the piperidine and quinoline nuclei are united by another carbon atom of the "second half," which appears as the methyl group in lepidine.

Hence the only point which still remains obscure in the constitution of the cinchona alkaloids is the mode of union of this carbon atom. In this connection Miller and Rohde have put forward a suggestion based on the hydrolytic decomposition of cinchonine and quinine, for which the original paper [4] must be consulted.

By means of moderate oxidation with chromic acid in acetic or sulphuric acid solution, Rabe [5] converted cinchonine and its isomeride cinchonidine into a ketone, which by analogy with tropinone was named

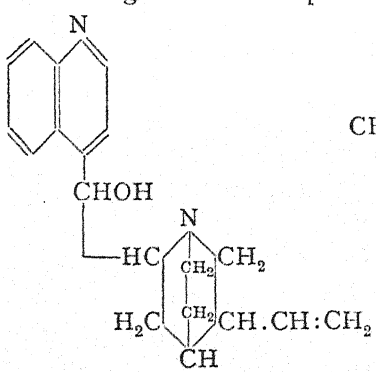
[1] P. Rabe and R. Ritter, *Ann.*, 1906, **350**, 180. [2] Skraup, *Monats.*, 1896, **17**, 368. [3] *Ber.*, 1907, **40**, 4679, 4711; 1909, **42**, 627. [4] Miller and Rohde, *Ber.*, 1894, **27**, 1279, 1187; 1895, **28**, 1056; 1900, **33**, 3214. [5] P. Rabe, *Ber.*, 1907, **40**, 3281, 3655; *Ann.*, 1909, **364**, 330.

cinchoninone. The corresponding compound, *quininone*, was obtained in a similar manner from quinine and its isomeride quinidine. The two tertiary nitrogen atoms and the vinyl group of the parent alkaloids are still present in these ketones, but the alcoholic hydroxyl group has disappeared, being changed into a ketonic group. Consequently, *cinchonine and quinine are secondary alcohols*.

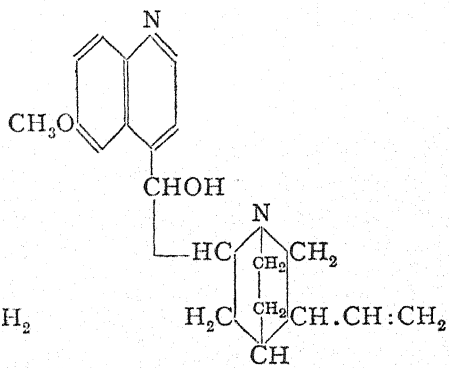
On reduction, cinchoninone and quininone are converted back into cinchonine and quinine, thus definitely establishing their relationship to the original alkaloids. In addition, it will be seen that information obtained from the chemical decomposition of the ketones [1] may be applied without modification to the cinchona alkaloids themselves.

Constitution of Quinine and Cinchonine

The investigations described in the foregoing pages led to the adoption of the following formulæ for quinine and cinchonine :—

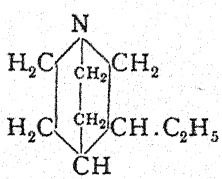


Cinchonine



Quinine.

Since each of the above formulæ contains three asymmetric carbon atoms, each structure represents a possibility of eight optically active and four racemic stereoisomerides.[2] Among these are **cinchonidine**, which is stereoisomeric with cinchonine, and **concinchinine**, a stereoisomeride of quinine.



β-Ethyl quinuclidine.

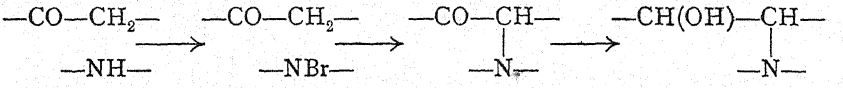
The possibility of the existence of a carbon bridge between the nitrogen atom and the 4-carbon atom of the piperidine nucleus, as shown above, has been established by the synthesis of **β-ethyl quinuclidine** [3] of the annexed structure. The parent compound quinuclidine has also been synthesised.[4]

Attempts to Synthesise the Cinchona Alkaloids

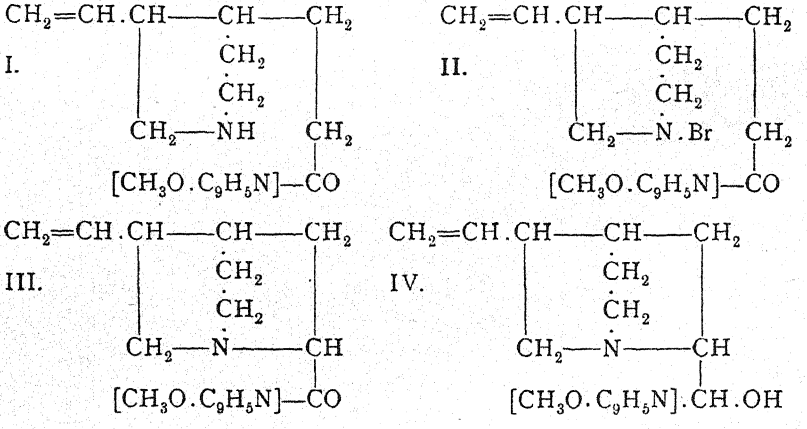
When cinchonine and quinine are heated for a long time with acetic acid, they undergo intramolecular change and yield *cinchotoxine* and

[1] P. Rabe, *Ann.*, 1909, **365**, 353. [2] For further details and for proposals concerning the rational nomenclature of the cinchona alkaloids and related compounds see P. Rabe, *Ber.*, 1922, **55**, 522. [3] Königs, *Ber.*, 1904, **37**, 3244. Königs and Bernhardt, *Ber.*, 1905, **38**, 3049. [4] Löffler and Stietzel, *Ber.*, 1909, **42**, 124.

quinotoxine respectively. These *toxines* are formed from the alkaloids by conversion of the —CHOH group into —CO, accompanied by the rupture of the quinuclidine nucleus. They are ketones as well as secondary bases. The reverse change from the toxines into the alkaloids has not been accomplished directly as yet, but has been effected indirectly through the following stages. The hydrogen atom of the imino group can be replaced by bromine to give bromo-imines, which by loss of a molecule of hydrogen bromide can be converted into the compounds quininone and cinchoninone [1] (see p. 749). These reactions lead to the regeneration of the quinuclidine nucleus peculiar to the cinchona alkaloids. Finally, the ketones can be reduced to the alkaloids themselves.



The partial synthesis of quinine from quinotoxine or quinicine [2] by this method proceeds as follows:—Quinicine (I) is converted into N-bromoquinicine (II) by the action of sodium hypobromite. Quininone (III) is obtained from the bromo-imine by treatment with alkali, and is then reduced to quinine (IV) by reduction in alcoholic solution, using aluminium powder in the presence of sodium ethylate.

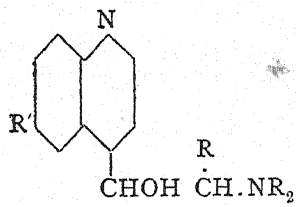


The above investigations established the position of the carbonyl group in the toxines, and revealed methods of opening up the quinuclidine nucleus of the alkaloids, as well as of converting the toxines so obtained back into the parent compounds. This measure of success paved the way for a number of attempts to synthesise cinchonine and quinine, and bases closely related to them. In every case the starting material was either cinchoninic acid, quininic acid, or an ester or nitrile of these acids. By making use of a convenient method of preparing cyano-quinolines, Kaufmann [3] succeeded in synthesising various acids and 4-quinolyl

[1] P. Rabe, *Ber.*, 1911, 44, 2088; 1913, 46, 1023, 1026. [2] P. Rabe and Kindler, *Ber.*, 1918, 51, 466. [3] *Ber.*, 1912, 45, 3090; 1913, 46, 57; 1916, 49, 2302. Synthesis of quininic acid, *Ber.*, 1909, 42, 3776; 1911, 44, 2061; 1912, 45, 1805; 1918, 51, 116; 1922, 55, 614. Also J. Halberkann, *Ber.*, 1921, 54, 3079, 3090.

ketones, and later obtained bases of the type V, which were closely related to the cinchona bases.

V.



R′ = H or alkyloxy group.

R = alkyl group.

The synthesis of cinchona alkaloids from derivatives of piperidine and quinoline has recently been completed by Rabe,[1] using cyano-quinolines and cinchoninic ester as his starting materials. From 4-methyl-pyridine (obtained from coal tar) Rabe synthesised cincho- and quino-toxines,[2] which, however, contained no vinyl group.

In conclusion, it may be mentioned that hydro-derivatives, such as dihydro-quinine (quinotine) and dihydro-cinchonine (cinchotine), which contain an ethyl group in place of the vinyl group of cinchonine and quinine, also occur in cinchona bark. They may be prepared from the last-named alkaloids by hydrogenation.[3]

Plasmoquine (p. 695) is a synthetic alkaloid having the constitution of a complex alkylamino-6-methoxy-quinoline. It acts directly on the schizomes of tropical malaria and is ten times as potent as quinine.

The Strychnos Alkaloids

There are three alkaloids in this series, namely strychnine, brucine and curarine. Whilst numerous investigations have been carried out on the first two of these compounds, **curarine**, on the other hand, has been very little examined from the chemical standpoint. In small doses it produces complete paralysis of the voluntary muscles.

Strychnine occurs in Ignatius beans (the seeds of *Strychnos Ignatii*), in the seeds of the fruit of *Strychnos nux vomica*, and in other sources.

It crystallises in rhombic prisms, which melt at 265°. It is very insoluble in water, has a bitter metallic taste, and is one of the most powerful poisons known. Regnault showed that the empirical formula of strychnine is $C_{21}H_{22}N_2O_2$. Although it contains two nitrogen atoms, it only forms stable salts with one equivalent of an acid. The decomposition of strychnine has been brought about by various methods, such as distillation with zinc dust, alkalis or alkaline earths, but the results obtained so far have given no certain information as to the carbon framework of the molecule, or the function of the oxygen and nitrogen atoms. The primary decomposition products of strychnine, however, indicate that one nitrogen atom is contained in a reduced quinoline or indole ring, and that its basic character is neutralised by union with a carbonyl group.

Tafel, who was the first to investigate strychnine, studied the action of methyl iodide and reducing agents on the alkaloid and its derivatives. He also examined the behaviour of strychnine towards nitric acid. More recently, investigations of strychnine and

[1] P. Rabe and co-workers, *Ber.*, 1913, **46**, 1024, 1026; 1917, **50**, 144; 1918, **51**, 1360.
[2] P. Rabe, K. Kindler and O. Wagner, *Ber.*, 1922, **55**, 532; and see also L. Ruzicka, *Helv. Chim. Acta*, 1921, **4**, 486. [3] P. Rabe, *Ber.*, 1911, **44**, 2088. A Skita, *Ber.*, 1912, **45**, 3588.

brucine have been carried out by Leuchs and by Robinson. The last named authors have proposed formulæ [1] for which the original literature should be consulted.

Brucine, $C_{23}H_{26}N_2O_4$, is generally found with strychnine in the wood and seeds of the various strychnos plants.

From hot water it crystallises in union with $4H_2O$, and from alcohol with $2C_2H_5OH$. The hydrated compound melts above 100° in its own water of crystallisation. When anhydrous it melts at 178°.

Brucine has the same physiological properties as strychnine, but is much less active. It also resembles strychnine in having two nitrogen atoms in its molecule and in being a monacid base. This similarity, taken with the fact that the two alkaloids occur together in nature, probably indicates a corresponding similarity in chemical constitution.

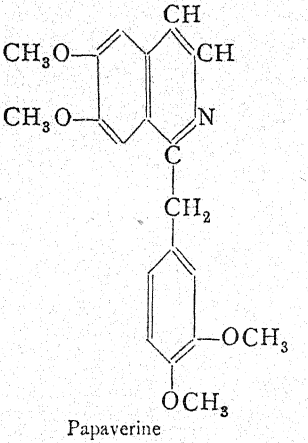
It has been shown that brucine contains two methoxyl groups, which can be estimated by Zeisel's method. In addition, Shenstone found that by the action of hydrochloric acid, methyl chloride is obtained from brucine but not from strychnine.

The formula for strychnine,[2] which is now established as $C_{21}H_{22}N_2O_2$, differs from that of brucine by the quantity $C_2H_4O_2$. Such a relationship would suggest that brucine is dimethoxy-strychnine. This has yet to be proved, however, and is chiefly supported by the frequent occurrence of the two alkaloids in one and the same plant, and by their similar physiological action.

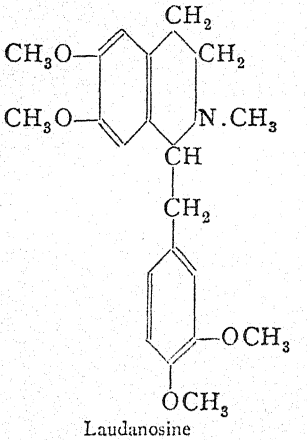
V.—ALKALOIDS OF THE ISOQUINOLINE GROUP

This group includes the five opium alkaloids, papaverine, laudanosine, laudanine, narcotine and narceine. All these are known to be related to isoquinoline, the first three being comparatively simple derivatives.

When it is remembered that the alkaloids hydrastine and berberine found in the root of *Hydrastis canadensis*, are also derived from isoquinoline, the importance of the latter as a parent compound of alkaloid bases becomes obvious.

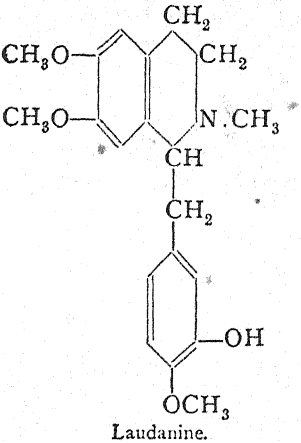


Papaverine



Laudanosine
(*d*-N-Methyl-tetrahydropapaverine)

[1] H. Leuchs, *Ber.*, 1932, **65**, 1230. B. K. Blount and R. Robinson, *J. C. S.*, 1932, 2305. For a summary of the position see H. King, *Ann. Rep. Chem. Soc.*, 1932, 200. [2] Attempts to synthesise strychnine derivatives have been made by Clemo, Perkin and Robinson, *J. C. S.*, 1924, **125**, 1751.

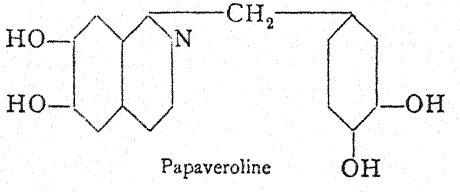


Laudanine.

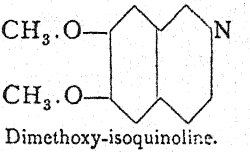
Papaverine, $C_{20}H_{21}NO_4$, occurs in opium in small quantities (0·8 to 1·0 per cent.) and crystallises in prisms which melt at 147°. It is almost insoluble in water or alkalis.

The constitution of papaverine (see p. 752) was established by G. Goldschmiedt,[1] from an examination of the manner in which the compound is decomposed by halogen acids, potassium permanganate and fused alkali.

When the alkaloid is heated with hydriodic acid four molecules of methyl iodide are liberated and *papaveroline* formed.



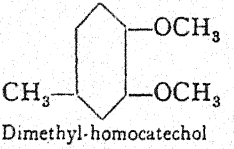
Papaveroline



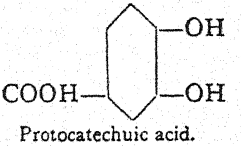
Dimethoxy-isoquinoline.

This reaction proves the presence of four methoxy groups in papaverine.

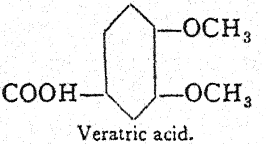
Decomposition of Papaverine on Fusion with Alkali.—When fused with potash, papaverine is decomposed into *dimethoxy-isoquinoline* and a compound which does not contain nitrogen. The latter has been shown to be *dimethyl-homocatechol*, as it yields *protocatechuic acid* on



Dimethyl-homocatechol



Protocatechuic acid.



Veratric acid.

[1] *Monats.*, 1883 to 1889.

more energetic treatment with potash. In addition, an appreciable quantity of *veratric acid* is always produced during the oxidation of the alkaloid. It will be observed that the side chains occupy the same positions in all these compounds.

Constitution of Papaverine.—Papaverine can therefore be looked upon as a combination of dimethoxy-isoquinoline and dimethyl-homocatechol.

$$\underset{\text{Dimethoxy-isoquinoline}}{C_{11}H_{11}NO_2} + \underset{\text{Dimethyl-homocatechol}}{C_9H_{12}O_2} = \underset{\text{Papaverine}}{C_{20}H_{21}NO_4} + H_2$$

The manner in which these two components are joined together was determined by Goldschmiedt in the following way.

Papaverine contains four methoxy groups, two of which are contained in each of the above disruption products. Since the components cannot be united through the methoxy-groups, they must be joined through a carbon atom of the benzene nucleus, or of the methyl group of dimethyl-homocatechol. The latter supposition is supported by the whole behaviour of papaverine, especially the ease with which the component parts can be separated. Hence the alkaloid is a substituted *phenyl-isoquinoline-methane*.

α-Carbo-cinchomeronic acid.

Finally, it was necessary to determine which carbon atom of the isoquinoline ring takes part in the union. This point is decided by the fact that *when papaverine is oxidised with potassium permanganate, α-carbo-cinchomeronic-acid* (2 : 3 : 4-pyridine tricarboxylic acid) *is formed.*

Synthesis of Papaverine

The synthesis of papaverine was accomplished by A. Pictet [1] and Gams, by the reactions summarised in the table on p. 755.

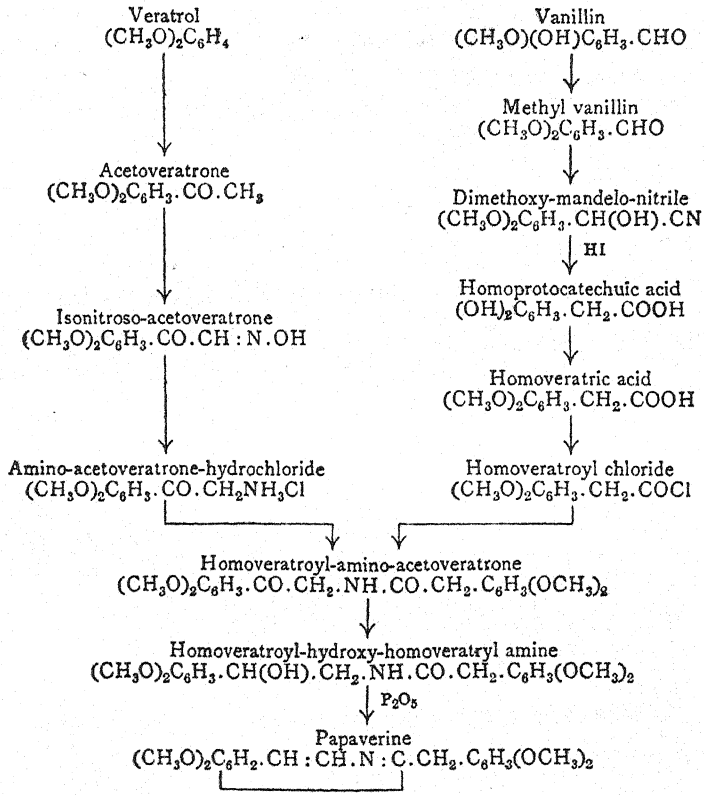
By the reduction of papaverine methochloride with tin and hydrochloric acid, Pictet and Athanasescu [2] obtained the racemic form of N-methyl-tetrahydro-papaverine. When this was resolved into its active components by means of quinic acid, the dextro-rotatory enantiomorph proved to be identical with the alkaloid **laudanosine** occurring in opium. The constitution of this alkaloid is therefore that given on p. 752. The narcotic properties of papaverine are not very marked, but they appear to be altogether absent in laudanosine. A complete synthesis of laudanosine may be effected in a manner similar to that employed for papaverine.[3]

Laudanine, which occurs in very small quantities in opium, was first investigated by Hesse and Goldschmiedt. Its constitution was finally solved by Späth,[4] who determined the position of the free phenolic hydroxyl group. It has been synthesised by Späth and Lang [5] (formula, see p. 753).

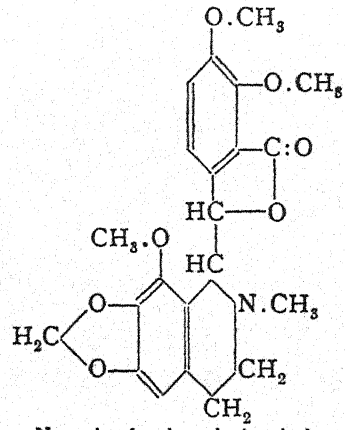
Narcotine, $C_{22}H_{23}NO_7$, is present as the free alkaloid in opium, in quantities varying from 0·75 to 9 per cent. After removing morphine

[1] A. Pictet and A. Gams, *Ber.*, 1909, **42**, 2943. See also K. W. Rosenmund, *Ber.*, 1927, **60**, 392; E. Späth, *Ber.*, 1927, **60**, 704. [2] Pictet and Athanasescu, *Ber.*, 1900, **33**, 2346. [3] A. Pictet and M. Finkelstein, *Ber.*, 1909, **42**, 1979. [4] Späth, *Monats.*, 1920, **41**, 297. [5] Späth and Lang, *Monats.*, 1921, **42**, 281.

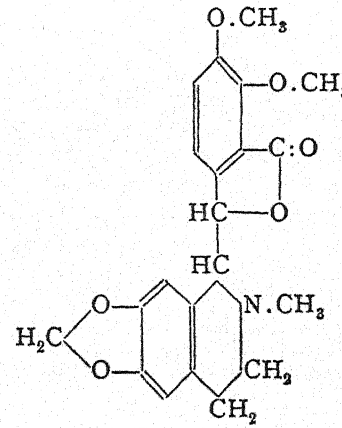
Synthesis of Papaverine.



Narcotine, Narceine and Hydrastine



Narcotine (methoxy-hydrastine)



Hydrastine.

and codeine from opium by extraction with water, narcotine is obtained by treating the residue with warm ether. It crystallises in rhombic prisms, m.p. 176°, and is insoluble in cold water or alkali. Narcotine is a *tertiary base*, and does not react with acetic anhydride. Hence the molecule contains *no free hydroxyl group*.

The presence of *three methoxyl groups* is shown by heating the alkaloid with hydrochloric acid, when it yields three molecular proportions of methyl chloride, together with *nornarcotine*, $C_{19}H_{17}NO_7$ or $C_{19}H_{14}NO_4(OH)_3$.

Narcotine is decomposed by potassium hydroxide at 220° with liberation of methylamine, dimethylamine and trimethylamine; the nitrogen atom is therefore attached to a methyl group.

Our knowledge of the constitution of narcotine is largely due to the work of Roser.[1]

Decomposition of Narcotine into Nitrogenous and Nitrogen-free Components

The decomposition of narcotine under the influence of reagents, such as water at 140°, dilute acids, and alkalis, has thrown valuable light on its constitution. Under this treatment it yields a nitrogen-free compound, *opianic acid*, and a base, *hydro-cotarnine*.

$$\underset{\text{Narcotine}}{C_{22}H_{23}NO_7} + H_2O = \underset{\text{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{Hydro-cotarnine.}}{C_{12}H_{15}NO_3}$$

With oxidising agents, *e.g.* nitric acid, platinic chloride, ferric chloride, or lead peroxide, narcotine decomposes in a similar manner to give *opianic acid* and *cotarnine*.

$$C_{22}H_{23}NO_7 + O + H_2O = \underset{\text{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{Cotarnine.}}{C_{12}H_{15}NO_4}$$

Reducing agents such as zinc and hydrochloric acid, and sodium amalgam, convert narcotine into *meconine*, which is a reduction product of opianic acid, and *hydro-cotarnine*.

$$C_{22}H_{23}NO_7 + H_2 = \underset{\text{Meconine}}{C_{10}H_{10}O_4} + \underset{\text{Hydro-cotarnine.}}{C_{12}H_{15}NO_3}$$

From these reactions it is evident that the molecule of narcotine consists essentially of two parts: a basic component corresponding to hydrocotarnine, and a nitrogen-free substance corresponding to opianic acid.

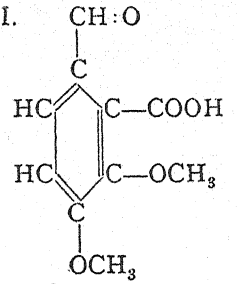
Once the structure of these individual parts had been determined, it was possible to build up the formula of narcotine itself.

Opianic acid was investigated by Beckett and Wright,[2] and by Wegscheider, and proved to be a carboxylic acid derived from dimethylprotocatechuic aldehyde. Its constitution is represented by formula I.

From a study of the products obtained by oxidation, and by interaction with methyl iodide, cotarnine has been assigned formula II (Roser). For an alternative formula see IV, p. 758.

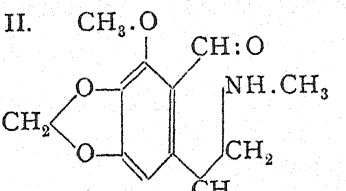
[1] Roser, *Ann.*, 1888, **245**, 311; **247**, 167; **249**, 156, 168; 1889, **254**, 334. [2] Beckett and Wright, *J. C. S.*, 1875, **28**, 583.

I.



Opianic acid.

II.

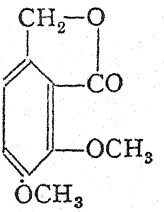


Cotarnine.

Meconine, formula III, has been shown to be the lactone of the alcohol corresponding to opianic acid.

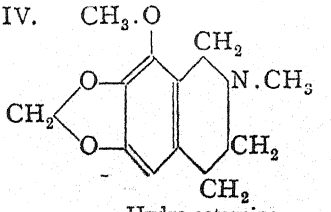
The conversion of cotarnine into hydro-cotarnine, by means of reducing agents, takes place by reduction of the aldehyde group —CHO to —CH_2OH, followed by the formation of an isoquinoline ring by elimination of water between the groups —CH_2OH and —$NHCH_3$. Hydro-cotarnine is therefore assigned formula IV.

III.



Meconine

IV.



Hydro-cotarnine.

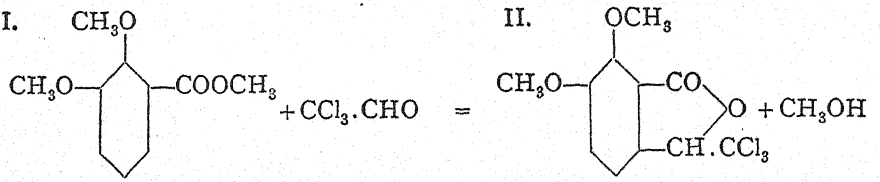
The constitution of the decomposition products opianic acid and meconine on the one hand, and cotarnine and hydro-cotarnine on the other, is therefore clear. The only point still to be decided is how the two component parts are linked together to form the alkaloid molecule.

In narcotine, $C_{22}H_{23}NO_7$, the hydro-cotarnine group cannot be united with opianic acid or meconine through one of the seven oxygen atoms, since five of these are already joined to alkyl groups (three to methyl and two to methylene) and the other two are both present in a lactone ring. Further, the valencies of the nitrogen atom are fully satisfied by the demands of the isoquinoline ring and the methyl group. The two components must therefore be connected through carbon atoms. There is no doubt that it is these carbon atoms which take up oxygen during the oxidation of the alkaloid and appear as aldehyde groups in opianic acid and cotarnine, since no aldehyde group is present in narcotine itself. For these reasons narcotine is given the constitution quoted on p. 755.

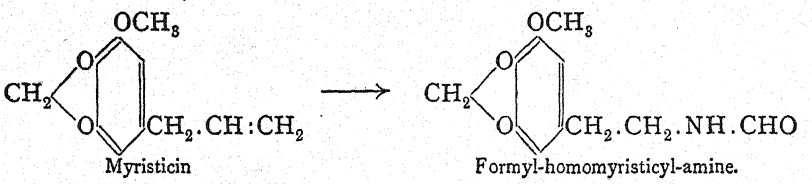
Synthesis of Narcotine.—Perkin and Robinson [1] showed that when meconine and cotarnine are boiled in alcoholic solution with potassium carbonate a compound is produced which is identical with the racemic alkaloid *gnoscopine*. By resolving this into its active components *d*- and *l*-narcotine were obtained, the *l*- variety being identical with the natural alkaloid.

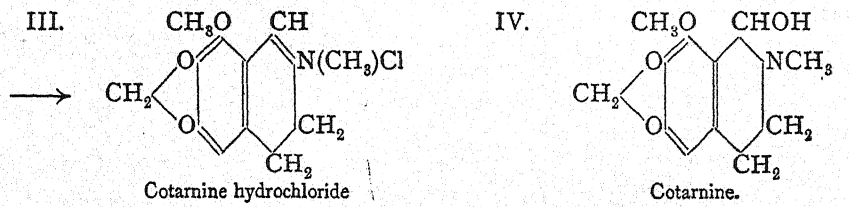
[1] *Proc. Chem. Soc.*, 1910, **26**, 46, 131.

Synthesis of Meconine.[1]—Guaiacol carboxylic acid, on methylation, was converted into the methyl ester of 2 : 3-dimethoxy-benzoic acid, I. The latter was condensed with chloral to give 5 : 6-dimethoxy-trichloromethyl phthalide, II, which was then hydrolysed to the corresponding phthalide carboxylic acid. The acid, on being heated, decomposed into carbon dioxide and meconine.



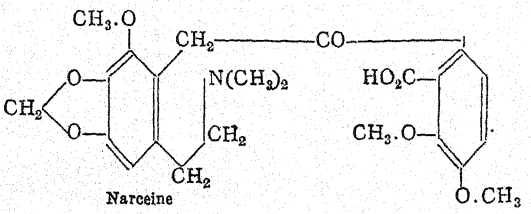
Synthesis of Cotarnine.—This base was synthesised by Salway, and later by Decker and Becker, from myristicin,[2] a constituent of oil of parsley and oil of nutmeg. An intermediate product in the later synthesis was formyl-homomyristicyl-amine. (Compare the preparation of hydrastinine from safrol.)





Spectroscopic investigations by Dobbie, Lauder and Tinkler[3] have shown that cotarnine salts correspond to the ammonium structure, III, but that the free base may exist either as the carbonium form, IV (in ether or chloroform solution), or as a mixture of the two forms (in aqueous or alcoholic solution).

Narceine is obtained by the action of alkali on narcotine methiodide. It is present in opium in small quantities (about 0·1 per cent.), and is a white crystalline compound



[1] Fritsch, *Ann.*, 1898, **301**, 352. [2] Salway, *J. C. S.*, 1910, **97**, 1208. Decker and Becker, *Ann.*, 1913, **395**, 328. [3] Dobbie, Lauder and Tinkler, *J. C. S.*, 1903, **83**, 598; 1904, **85**, 121.

of melting-point 171°. It has the preceding structure, and is formed from narcotine by the rupture of the pyridine and lactone rings.

Hydrastine (see formula on p. 755) occurs in the root of *Hydrastis canadensis* L., a plant belonging to the Ranunculaceæ and indigenous to North America. It crystallises in prisms, m.p. 135°. The extract of *Hydrastis canadensis* is used therapeutically in cases of uterine hæmorrhage.

The structure of hydrastine, which was established by the work of Freund [1] and E. Schmidt,[2] is very similar to that of narcotine.

When hydrastine is oxidised with potassium permanganate in acid solution, *opianic acid* is formed. (Compare Narcotine, p. 756.)

On oxidation with dilute nitric acid at 50° to 60°, however, hydrastine yields, in addition to opianic acid, a basic compound of the formula $C_{11}H_{13}NO_3$, known as *hydrastinine*.

$$\underset{\text{Hydrastine}}{C_{21}H_{21}NO_6} + H_2O + O = \underset{\text{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{Hydrastinine.}}{C_{11}H_{13}NO_3}$$

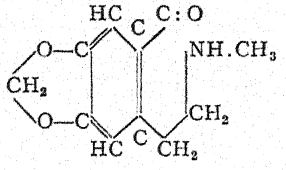
The difference of CH_2O between the molecules of cotarnine and hydrastinine, the basic decomposition products of narcotine and hydrastine respectively, indicates that cotarnine is a methoxy-hydrastinine. Narcotine must therefore be a methoxy-hydrastine with the methoxyl group attached to the basic part of the molecule. This conclusion has been confirmed by the determination of the methoxyl group by Zeisel's method (E. Schmidt).

Hydrastinine is of the greatest importance in connection with the constitution of hydrastine. Its structure has been ascertained both by degradation and synthesis.

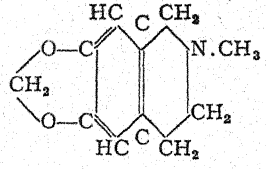
Synthesis of Hydrastinine

Hydrastinine (V) is a derivative of piperonal, containing a basic side chain in the ortho-position to the aldehyde group. When it is reduced with zinc and hydrochloric acid, ring formation takes place with loss of oxygen and production of hydro-hydrastinine (VI). This compound is an isoquinoline derivative and formed an intermediate product in the first synthesis of hydrastinine to be effected.[3]

V.



VI.



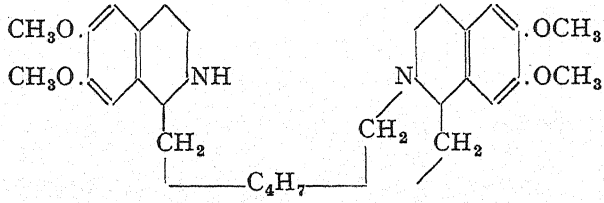
Emetine and Cephalein

Ipecacuanha has long been used medicinally as an emetic and purgative and also more recently in cases of amœbic dysentery. Pelletier in 1817 identified its most important active principle as the base **emetine.**

[1] M. Freund, *Ann.*, 1892, **271**, 311. [2] E. Schmidt, *Archiv. der Pharm.*, 1893, **231**, 541. [3] Fritsch, *Ann.*, 1895, **286**, 18. For syntheses of hydrastinine see Decker, *Ann.*, 1913, **395**, 321; also Rosenmund, *J. C. S.*, 1919, A, i, 280; Buck, Perkin and Stevens, *J. C. S.*, 1925, **127**, 1462.

In addition, ipecacuanha contains **cephalein**, *psychotrine*, o-*methyl-psychotrine* and *emetamine*, all of which stand in close relationship to one another.[1] Within the last few years Späth [2] has partially elucidated the structure of emetine and cephalein. Emetine is an O-methyl-cephalein; these two bases have thus similar constitutions.

Emetine contains two 6 : 7-dimethoxy-1 : 2 : 3 : 4-tetrahydro-isoquinoline complexes and has been assigned the following skeleton formula by Späth:

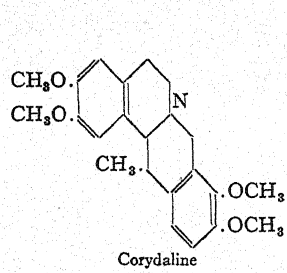


The structure of the residue C_4H_7 between the two cyclic groups is not yet determined.

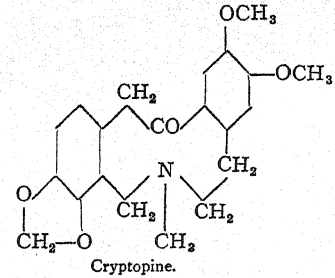
Cephalein possesses a similar constitution to emetine, but has a phenolic hydroxyl in place of a methoxyl group.

Corydalis Alkaloids

A large number of alkaloids are present in the bulbous rhizomes of *Corydalis cava*, belonging to the Papaveraceæ family, which in this respect is a worthy counterpart of *Papaver somniferum*, the source of the opium alkaloids. At least fifteen alkaloids have been discovered in the corydalis group, our knowledge of them being chiefly due to Gadamer, who has subdivided them into the corydaline, bulbocapnine and corycavine groups. The members of the corydaline group are closely related to hydroberberine, and those of the bulbocapnine group to apomorphine. The latter undoubtedly contain a phenanthrene nucleus and must therefore be regarded as members of the phenanthrene group of alkaloids. The constitution of the corycavine group is not known with sufficient certainty to show whether this group is directly related to corydaline or bulbocapnine.



Corydaline



Cryptopine.

The constitutions of cryptopine and protopine have been established by W. H. Perkin, jun., and co-workers.[3] By replacing the two methoxyl groups at the top right-hand side of the above cryptopine formula by a methylene ether group (O—CH_2—O) the structure of protopine is obtained.[3]

[1] For earlier references see Karrer, *Ber.*, 1916, **40**, 2058. [2] E. Späth and W. Leithe, *Ber.*, 1927, **60**, 688. See also W. H. Brindley and F. L. Pyman, *J. C. S.*, 1927, 1067. [3] R. D. Haworth and W. H. Perkin, jun., *J. C. S.*, 1926, 1769. See also *Chem. Soc. Ann. Rep.*, 1928, 169, 187 *et seq.*

Up to the present the following individual bases have been isolated:

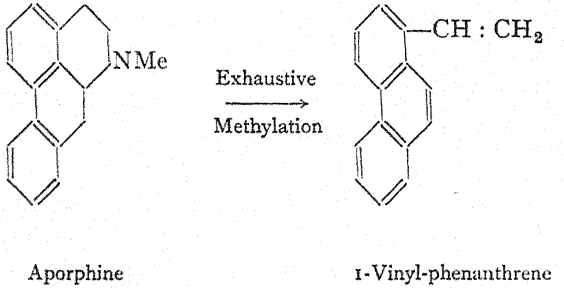
1. Corydaline	$C_{22}H_{27}NO_4$	9. Bulbocapnine	$C_{19}H_{19}NO_5$
2. Corybulbine	$C_{24}H_{25}NO_4$	10. Corydine	$C_{20}H_{23}NO_4$
3. Isocorybulbine	$C_{21}H_{25}NO_4$	11. Corypalmine	$C_{20}H_{23}NO_4$
4. Dehydrocorydaline	$C_{22}H_{24}NO_4 \cdot OH$	12. Corytuberine	$C_{19}H_{21}NO_4$
5. Corycavine	$C_{23}H_{23}NO_6$	13. Glaucine	$C_{21}H_{25}NO_4$
6. Corycavamine	$C_{21}H_{21}NO_5$	14.	$C_{21}H_{21}NO_8$
7. Corycavidine	$C_{22}H_{25}NO_5$	15. Protopine	$C_{21}H_{22}NO_7$
8.	$C_{20}H_{19}NO_5$		

Most of these alkaloids are similar to morphine in their physiological properties and effect on the heart, but as yet they are not used in medicine. For information as to their constitution the original papers must be consulted.[1]

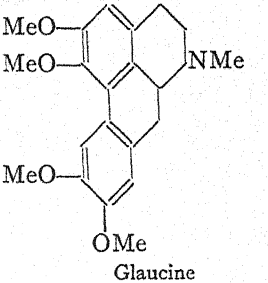
VI.—ALKALOIDS OF THE PHENANTHRENE GROUP

Aporphine Group

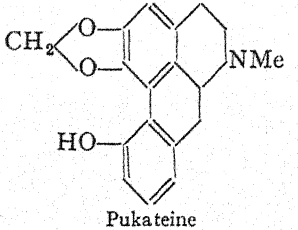
A number of the above-mentioned alkaloids, including glaucine, bulbocapnine and corytuberine are derivatives of aporphine, a base containing a condensed phenanthrene-pyridine structure. Glaucine and aporphine [2] have been synthesised by Gadamer; they are represented by the following abbreviated formulæ, in which the normal benzenoid nuclei are to be distinguished from the hydrogenated rings. (Me = methyl group.)



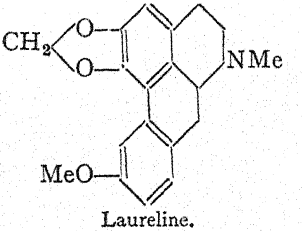
Aporphine — 1-Vinyl-phenanthrene



Glaucine



Pukateine



Laureline.

Barger and his co-workers have established further examples of this type in laurotetanine [3] (from various Lauraceæ) and in pukateine and laureline [4] (from the bark of the Pukatea, Laurelia Novæ Zealandiæ).

[1] Gadamer, *Arch. d. Pharm.*, 1902, **240**, 19, 51; 1911, **249**, 423, 487, 518; 1916, **254**, 295. Feist, *ibid.*, 1908, **245**, 586; Asahina, *ibid.*, 1909, **247**, 202. E. Späth and Lang, *Ber.*, 1921, **54**, 3074. [2] *Arch. Pharm.*, 1925, **263**, 81. [3] Barger and co-workers, *Ber.*, 1933, **66B**, 450. [4] G. Barger and A. Girardet, *Helv. Chim. Acta*, **1931**, 481.

From their general properties and behaviour on oxidation the last two compounds have been assigned the above constitutions. In physiological action they resemble morphine.

When submitted to exhaustive methylation aporphine yields 1-vinyl-phenanthrene. The methoxyl derivatives under similar treatment are converted into the corresponding 1-vinyl-methoxy-phenanthrenes.

Morphine Alkaloids

Morphine, Codeine and Thebaine

It has been definitely proved that the alkaloids morphine, codeine and thebaine contain a phenanthrene nucleus, but the nature of the nitrogen ring is not yet known with certainty. The idea originally advanced by Knorr, that they are derived from morpholine (p. 245), has now been abandoned. From the investigations of Pschorr it is probable that these compounds, like those in the previous section, contain an isoquinoline ring, but other possibilities are not excluded. Hence the usual method of classification, according to the basic complex present, cannot be adopted here.

Morphine is the chief basic constituent of opium, in which it is present in quantities varying from 3 to 23 per cent. It was the first alkaloid to be isolated from a plant source, and its discovery by the apothecary Sertürner, in 1806, has been of great value to pharmacology and the development of organic chemistry. Its composition was shown by Laurent to correspond to the formula $C_{17}H_{19}NO_3+H_2O$.

Morphine crystallises from alcohol in small prisms which melt with decomposition at 230°. It dissolves sparingly in water, is odourless, has a bitter taste and is laevorotatory.

The hydrochloride, $C_{17}H_{19}NO_3$, $HCl+3H_2O$, *morphinæ hydrochloricum*, crystallises in fine silky needles. It is widely used as a soporific and for the alleviation of pain. Solutions of morphine and its salts give a dark blue coloration with ferric chloride; a solution of the alkaloid in concentrated sulphuric acid is coloured blood-red on the addition of a little nitric acid.

Codeine also occurs in opium, but in smaller quantities (0·3 to 2 per cent.) than morphine. From this source it was isolated by Robiquet in 1832. Gerhardt proved the formula of codeine to be $C_{18}H_{21}NO_3,H_2O$, from which it was concluded to be a homologue of morphine. It is generally prepared from the latter compound.

Codeine crystallises in prisms or in octahedra of the rhombic system; it melts at 153° and is sparingly soluble in water or alkalis. It is laevorotatory, very poisonous and possesses a somewhat bitter taste. Like morphine it is a narcotic. Codeine and similarly constituted compounds are of greater medicinal value than morphine, on account of their sedative action and the fact that they reduce irritation of the air passages; hence they exert a favourable influence on respiration. Codeine is therefore a

valuable specific in the treatment of coughs. Codeine methobromide is used under the name of *eucodine*.[1]

Thebaine, which crystallises in silvery plates of melting-point 193°, is present in opium in quantities varying from 0·2 to 1 per cent.

A comparison of the formulæ of morphine, codeine and thebaine suggests that these compounds are closely related to one another. This is supported by the common occurrence of the three bases in opium, and by the results of experimental investigation.

$C_{17}H_{19}NO_3$	$C_{18}H_{21}NO_3$	$C_{19}H_{21}NO_3$
Morphine	Codeine	Thebaine.

For this reason it is convenient to discuss morphine, codeine and thebaine in connection with one another. Owing to their greater practical importance, morphine and codeine will be treated in more detail.

Action of Dehydrating Agents on Morphine

Oxalic acid, sulphuric acid, hydrochloric acid, phosphoric acid, alkalis and concentrated solutions of zinc chloride may act on morphine in two ways. Sometimes condensation takes place with the formation of compounds such as *trimorphine* and *tetramorphine*, and sometimes water is eliminated according to the equation

$$\underset{\text{Morphine}}{C_{17}H_{19}NO_3} = H_2O + \underset{\text{Apomorphine.}}{C_{17}H_{17}NO_2}$$

The compound **apomorphine** is an amorphous, sparingly soluble base, which readily undergoes oxidation. In physiological action it differs entirely from morphine; it has no narcotic properties but is a powerful emetic. For its constitution see p. 771.

Functions of the three Oxygen Atoms in Morphine. Relationship of Morphine to Codeine

The three oxygen atoms of morphine possess different functions. One of them is present in a phenolic hydroxyl group, which endows the alkaloid with certain acidic properties. The hydrogen of this group is replaceable by metals and by acyl and alkyl radicals; in codeine it is replaced by a methyl group.

Codeine is therefore a methyl ether of morphine. This relationship between the two alkaloids was recognised by Matthiessen and Wright in 1869,[2] and represented by them as follows:

$C_{17}H_{17}NO(OH)_2$	$C_{17}H_{17}NO(OH)(OCH_3)$
Morphine	Codeine.

By the action of concentrated hydrochloric acid on codeine at 100° they obtained an amorphous chlorinated derivative, *chlorocodide*.

$$\underset{\text{Codeine}}{C_{18}H_{21}NO_3} + HCl = \underset{\text{Chlorocodide.}}{C_{18}H_{20}ClNO_2} + H_2O$$

When this was heated with water at 130° codeine was regenerated. With hydrochloric acid at 150°, on the other hand, it was decomposed into apomorphine and methyl chloride.

$$\underset{\text{Chlorocodide}}{C_{18}H_{20}ClNO_2} = \underset{\text{Apomorphine.}}{C_{17}H_{17}NO_2} + CH_3Cl$$

[1] *C.*, 1905, II, 785.

[2] *Proc. Roy. Soc.*, 1869, 17, 364.

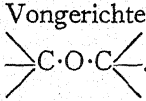
On combining these two equations, it is seen that hydrochloric acid decomposes codeine at 150° with elimination of a methyl group and a molecule of water. The solid reaction product is identical with that which results from morphine by the action of dehydrating agents. Hence codeine must be derived from morphine by the replacement of a hydroxyl group by a methoxyl group.

The conversion of morphine into codeine, which was effected in 1881 by Grimaux, confirmed the conclusions of Matthiessen and Wright, and definitely proved that codeine was the monomethyl ether of morphine. Grimaux prepared codeine from morphine by treating the latter with methyl iodide in the presence of alkali.

$$\underset{\text{Morphine}}{C_{17}H_{17}NO(OH)_2}+CH_3I+KOH = KI+H_2O+\underset{\text{Codeine.}}{C_{17}H_{17}NO(OH)(OCH_3)}$$

The constitutions of these two alkaloids may thus be discussed together.

The *second oxygen atom in morphine* has been shown by Hesse to be present in an alcoholic grouping >CH.OH, since codeine on oxidation yields a ketone *codeinone*.

The *third oxygen atom* is very non-reactive. According to Vongerichten,[1] it is united to two carbon atoms, as in the ethers  .

Roser and Howard, by the use of Zeisel's method, proved that *thebaine* contains two methoxyl groups. Thus the relationship between the three alkaloids may be represented as follows :—

				Non-reactive oxygen	Phenolic hydroxyl.	Alcoholic hydroxyl.
Morphine	C_{17}	H_{16}	N	O	OH	HOH
Codeine	C_{17}	H_{16}	N	O	OCH_3	HOH
Thebaine	C_{17}	H_{14}	N	O	OCH_3	$HOCH_3$

Function of the Nitrogen Atom in Morphine

The behaviour of morphine on *exhaustive methylation*[2] shows that the nitrogen atom is contained in a ring, and that it is attached to three carbon atoms and therefore tertiary. Morphine unites directly with one molecule of methyl iodide to give a methiodide.

When methyl-morphine methiodide (*i.e.* codeine methiodide) is heated with caustic soda it is readily converted into a tertiary base, **methyl-morphimethine** (Hesse).

$$C_{17}H_{17}O(OH)(OCH_3):N\begin{matrix}CH_3\\ \diagup\\ \diagdown\\ OH\end{matrix} = H_2O+C_{17}H_{16}O(OH)(OCH_3):N.CH_3$$

This reaction resembles the transformation of dimethyl-piperidinium hydroxide into pentenyl-dimethylamine (see p. 686), a change which necessarily involves the disruption of the piperidine ring. Hence it may

[1] *Ann.*, 1881, **210**, 105. [2] Knorr, *Ber.*, 1889, **22**, 182.

be concluded that the formation of methyl-morphimethine is due to the rupture of the nitrogen ring of morphine.

Methyl-morphimethine exists in different isomeric forms and is a tertiary base, reacting only with one molecule of methyl iodide, to give a methiodide.[1] Its constitution will be discussed more fully later.

Thebaine is also a tertiary base and yields a methiodide of the formula $C_{19}H_{21}NO_3,CH_3I$.

Arrangement of the Carbon Atoms in Morphine

Of the 17 carbon atoms in the morphine molecule 14 must belong to a phenanthrene nucleus, since the non-nitrogenous decomposition products of the alkaloid have always proved to be phenanthrene derivatives.

Phenanthrene itself was isolated by Schrötter and Vongerichten by the distillation of the alkaloid with zinc dust. Knorr obtained it in the same way from methyl-morphimethine.

Decomposition of Morphine, Codeine and Thebaine

The decomposition of morphine and its derivatives into nitrogenous compounds of low carbon content and nitrogen-free compounds, which are rich in carbon, may be accomplished in various ways, *e.g.* 1. By the action of hydrochloric acid or acetic anhydride on the metho-hydroxides of morphine and codeine, or on methyl-morphimethine. 2. By decomposition of the ammonium bases of the morphine group under the influence of heat or alkalis.

Decomposition Products of Morphine which do not contain Nitrogen

The degradation products obtained by method 1 are derivatives of the compound *morphol*, $C_{14}H_8(OH)_2$, described on pp. 572 *et seq.*; those obtained by method 2 are derived from the phenolic compound *morphenol*, see pp. 573, 575.

The constitution of these two compounds has been established chiefly through the analytical researches of Vongerichten and the syntheses of Pschorr.

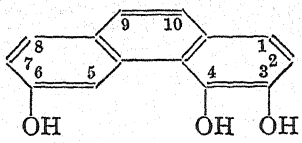
Morphol has been identified as 3 : 4-dihydroxy-phenanthrene, and this constitution has been confirmed by the synthesis carried out by Barger [2] (p. 573).

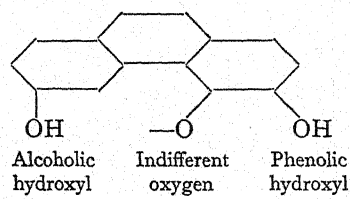
Pschorr and Vogtherr [3] prepared the acetyl derivative of 3-methoxy-4-hydroxy-phenanthraquinone by method 5 described on p. 569, and found it to be identical with the acetyl derivative of methyl morpholquinone which Vongerichten had previously obtained by heating methylmorphimethine with acetic anhydride.

Thus the methoxyl group in codeine and the phenolic hydroxyl group in morphine each occupies position 3 in the phenanthrene nucleus. The further question as to whether the hydroxyl group in position 4 in the decomposition products corresponds to the indifferent oxygen atom or

[1] Knorr, *Ber.*, 1902, 35, 3012. [2] Barger, *J. C. S.*, 1918, 113, 218. [3] *Ber.*, 1902, 35, 4412.

to the alcoholic hydroxyl of morphine was decided by Knorr [1] in favour of the former assumption. He was able to show that one of the decomposition products of codeinone—a ketone obtained by the oxidation of codeine—is 3-methoxy-4 : 6-dihydroxy-phenanthrene, and concluded that the alcoholic hydroxyl group is attached to position 6. Hence the alkaloids morphine and codeine are derivatives of 3 : 4 : 6-trihydroxy-phenanthrene. From the investigations of thebaol and codeinone to be described later, it also follows that thebaine is derived from the same compound. The functions of the three oxygen atoms in morphine may thus be indicated as follows :—





Nitrogenous Decomposition Products of Morphine and the Decomposition Products of Thebaine

Our knowledge of the nitrogenous decomposition products of morphine is chiefly due to the investigations of Knorr.[2]

The *decomposition of methyl-morphimethine* has given results of such importance that this compound may be considered the key to the constitution of morphine.

By the decomposition of methyl-morphimethine metho-hydroxide under the influence of heat, the volatile basic decomposition product was found to be trimethylamine. When treated with acetic anhydride the compound gave dimethylamine. Hence, of the three carbon atoms which lie outside the phenanthrene nucleus in morphine, one must be united to nitrogen in the form of a methyl group.

Methyl-morphimethine was found to be decomposed by acetic anhydride to give the basic products *dimethylamine* and the acetyl derivative of *hydroxyethyl-dimethylamine*, $HO.CH_2.CH_2.N(CH_3)_2$.

The isolation of hydroxyethyl-dimethylamine gave rise to the erroneous conclusion that in methyl-morphimethine the phenanthrene component and hydroxyethyl-dimethylamine are linked together through the oxygen atom of the base, and led Knorr to advance the " oxazine " or " morpholine formula " for morphine.

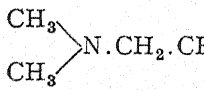
From thebaine, in a similar manner, Freund [3] obtained *acetoxyethyl-methylamine*, $CH_3CO.O.CH_2.CH_2.NH.CH_3$, and acetyl-thebaol. The latter was identified by Pschorr [4] as 3 : 6-dimethoxy-4-acetoxy-

[1] Knorr, *Ber.*, 1903, **36**, 3074. [2] Knorr, *Ber.*, 1889, **22**, 181, 1113, 2081 ; *Ber.*, 1894, **27**, 1144 ; *Ber.*, 1904, **37**, 3494, 3499 ; *Ber.*, 1905, **33**, 3172. [3] Freund, *Ber.*, 1897, **30**, 1357. [4] Pschorr, *Ber.*, 1902, **35**, 4401.

phenanthrene (see p. 575), thus proving that the two methoxy groups in thebaol, and therefore also in thebaine, occupy positions 3 and 6.

In an attempt to isolate any intermediate compound which might be formed during this decomposition, Pschorr and Haas [1] investigated the action of benzoyl chloride on thebaine at 0°. The degradation of the alkaloid was found to take place very smoothly under such conditions, with the formation of the *benzoyl derivatives of thebaol* and *hydroxyethyl-methylamine*.

The above oxazine or morpholine formula had to be abandoned after the discovery that the complex .C.C.N: could be detached from the morphine molecule as *ethyl dimethylaminoethyl ether*,



by heating methyl-morphimethine with sodium methoxide, or thebaine and codeinone methiodides with alcohol.

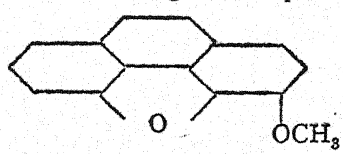
The above ether-base, however, is not a primary decomposition product. Knorr suggests that the three-membered chain of the side ring is first removed from the morphine alkaloids in the form of an unsaturated compound, probably as *vinyl-dimethylamine* $(CH_3)_2N.CH:CH_2$, which at once combines with alcohol to give the ether-base.[2]

$$(CH_3)_2N.CH:CH_2+C_2H_5OH = (CH_3)_2N.CH_2.CH_2.O.C_2H_5$$

Should this prove correct, then the acetyl derivatives of the alcohol bases, obtained by the action of acetic anhydride on methyl-morphimethine, thebaine and codeine, must be regarded as secondary addition products of acetic acid with a compound which does not contain oxygen. In this case the formation of the hydramines cannot be due, as was formerly suggested, to a hydrolytic decomposition in which the "indifferent" oxygen of the original alkaloid is converted into the hydroxyl group of the alcohol base.

These views have received support from the observations of Knorr and Pschorr, who found that meta-thebainone [3] is decomposed by acetic anhydride with the formation of hydroxyethyl-dimethylamine, thus behaving similarly to methyl-morphimethine, even though it no longer contains an indifferent oxygen atom.

For these reasons the assumption of an oxazine ring in morphine and thebaine has proved untenable, and there is no doubt that the indifferent oxygen atom in the morphine alkaloids is present in a furane ring, forming a bridge between positions 4 and 5 of the phenanthrene nucleus. A similar structure is found in methyl-morphenol, which is a

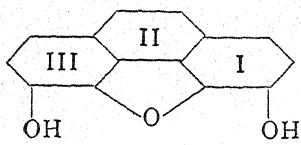


[1] Pschorr and Haas, *Ber.*, 1906, **39**, 16. [2] L. Knorr, *Ber.*, 1904, **37**, 3500, 3507.
[3] **Meta-thebainone** (formerly called thebainone) is a ketone obtained by reducing thebaine with stannous chloride and hydrochloric acid (Pschorr, *Ber.*, 1905, **38**, 3160). It was also isolated by Knorr by the reduction of codeinone (*Ber.*, 1905, **38**, 3171), hence the ketonic oxygen is in position 6 in the phenanthrene nucleus.

decomposition product of methyl-morphi-methine (Vongerichten). *The complex* $>(C_2H_4NCH_3)$ *is therefore attached to the phenanthrene nucleus in methyl-morphimethine and the morphine alkaloids by means of a carbon linking.*

The same conclusion was arrived at by Freund [1] from a study of the *action of organo-magnesium halides on thebaine.* From the course of these reactions Freund concluded that of the three oxygen atoms in thebaine, of which two are present in methoxy groups, the third belongs to a ring similar to that occurring in diphenylene oxide. Hence the complex attached to the phenanthrene nucleus is not $-O.CH_2.CH_2.N.CH_3$ but $-CH_2.CH_2.N.CH_3$. Freund therefore expressed the structure of thebaine by a formula [2] similar to III p. 770, in which, however, the ethanamine chain is attached to a different position (C 5, see p. 769).

Knorr and Pschorr [3] summarise their views on the constitution of the morphine alkaloids in the following statements :



1. The three morphine alkaloids are derivatives of 3 : 6-*dihydroxy-phenanthrylene oxide.*

In morphine the hydroxyl groups are present as such, in codeine one of them is methylated, and in thebaine both are methylated.

2. Attached to the phenanthrene nucleus as a side ring is the divalent complex $-C_2H_4-N(-CH_3)-$.

3. The nucleus present in thebaine is tetrahydro-phenanthrene, whilst that in morphine and codeine is hexahydro-phenanthrene. The six additional hydrogen atoms in morphine are distributed between rings II and III, whereas ring I, to which the phenolic hydroxyl group is attached, possesses true aromatic properties. From the course of the degradation it appears that the complex $-C_2H_4.N.CH_3$ belongs to the reduced part of the phenanthrene nucleus.

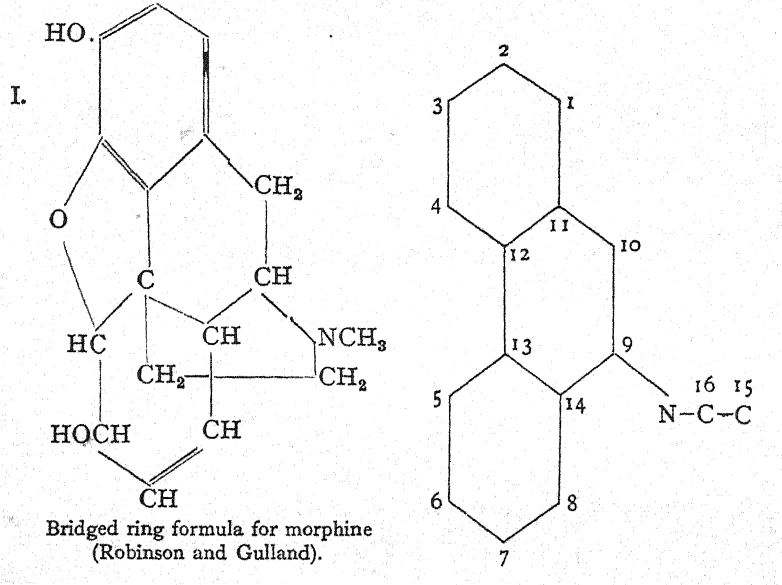
A consideration of all the available facts led Knorr [4] to put forward a formula for morphine in agreement with that advanced by Faltis a year earlier,[5] and which differed from formula I, p. 769, in having the double bond at 8 : 14 instead of 7 : 8, and the ethanamine chain attached to C 5 in place of C 13.

Although these formulæ satisfy most of the experimental facts, there are a number of points which they fail to explain.

The points still at issue are the position of the double bond and the

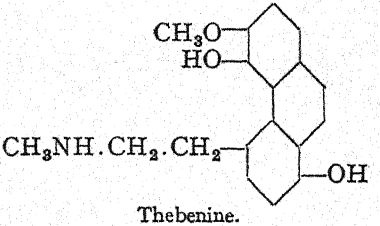
[1] *Ber.*, 1905, 38, 3234. [2] M. Freund, *Ber.*, 1916, 49, 1299. Freund and Speyer, *Z. ang. Ch.*, 1917, 30, 530. [3] L. Knorr and R. Pschorr, *Ber.*, 1905, 38, 3176. [4] Knorr, *Ber.*, 1907, 40, 3341. [5] Faltis, *J. C. S.*, 1906, A, i, 979. Direct experimental evidence for the existence of a double bond in codeine is provided by oxidation of the latter to the glycol, dihydroxy-dihydro-codeine, on treatment with dilute aqueous permanganate (R. S. Cahn and R. Robinson, *J. C. S.*, 1926, 908).

mode of attachment of the carbon end of the C—C—N chain to the phenanthrene nucleus. In 1925 it was suggested independently by Gulland and Robinson,[1] and by Wieland and Kotake,[2] that the double bond in morphine and codeine should be allocated to position 7 : 8 instead of 8 : 14 as in Knorr's formula. Further confirmation of this new arrange-



Bridged ring formula for morphine (Robinson and Gulland).

ment was given by the investigation carried out by van Duin, Robinson and Smith[3] on *neopine*, a comparatively rare alkaloid found in opium, which has been shown to be an isomer of codeine having the double bond in the 8 : 14-position. In 1923 Gulland and Robinson[4] advanced arguments in favour of a C 13 or C 14 linkage for the ethanamine side chain, a modification which is supported indirectly by Schöpf's proof[5] that the union is not in the C 5 position, and also by the direct experimental work of Wieland and Small[6] and Gulland.[7] Robinson and Gulland's formula for morphine is now generally accepted.[5,8]



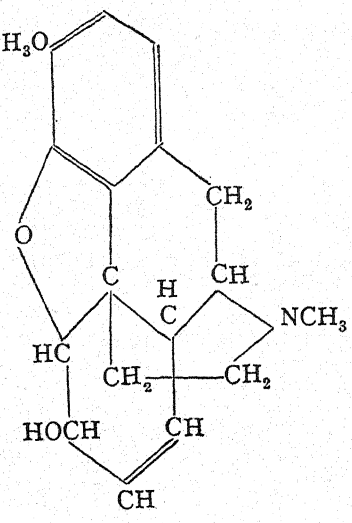
Thebenine.

The final choice between C 13 and C 14 is complicated by the surprising migrations which may occur in the alkaloids of this group under relatively mild experimental conditions, leading to the formation of derivatives containing substituents at C 5, C 13 or C 14. For example, thebaine on being heated for a short time with dilute

[1] J. M. Gulland and R. Robinson, *Manchester Lit. and Phil. Soc.*, 1925, No. 10. *Nature*, 1925, 115, 625. [2] Wieland and Kotake, *Ann.*, 1925, 444, 69; *Ber.*, 1925, 58, 2009. [3] van Duin, Robinson and Smith, *J. C. S.*, 1926, 903. [4] Gulland and Robinson, *J. C. S.*, 1923, 980, 998. [5] Schöpf, *Ann.*, 1927, 452, 211. [6] Wieland and Small, *Ann.*, 1928, 467, 17. [7] J. M. Gulland, *J. C. S.*, 1928, 702. [8] J. v. Braun and R. S. Cahn, *Ann.*, 1926, 451, 55.

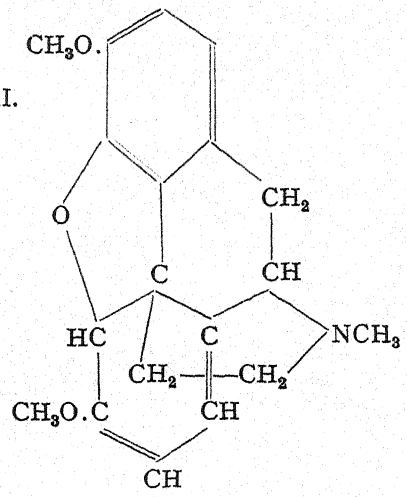
hydrochloric acid yields *thebenine*, in which the C—C—N chain is found attached to the 5-position.[1] On the whole, however, the evidence indicates C 13 as the most probable point of attachment, as in formula II.

II.



Codeine
(Gulland and Robinson).

III.

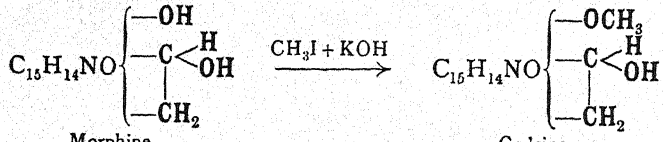


Thebaine.
(Gulland and Robinson).

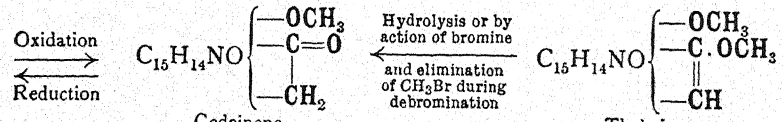
Thebaine is a less hydrogenated alkaloid represented by Gulland and Robinson as having formula III, identical with that of Knorr except for the different point of union of the C—C—N chain. The formula is supported by Schöpf's reduction of thebaine to tetrahydro-thebaine. [2]

Conversion of Thebaine into Codeine

As has already been explained, thebaine resembles morphine and codeine in constitution, but represents a different degree of hydrogenation of the phenanthrene nucleus. Attempts were therefore made to establish an experimental connection between these two structures.



Morphine. Codeine.



Codeinone Thebaine.

This was successfully accomplished by Knorr [3] through the compound

[1] Knorr, *Ber.*, 1903, **36**, 3074. Pschorr, *ibid.*, 1904, **37**, 2780; 1907, **40**, 2001; *Ann.*, 1910, **373**, 51, 77. J. M. Gulland and C. J. Virden, *J. C. S.*, **1928**, 921. [2] Schöpf, *loc. cit.*
[3] L. Knorr, *Ber.*, 1906, **39**, 1409. Freund, *Ber.*, 1906, **39**, 844.

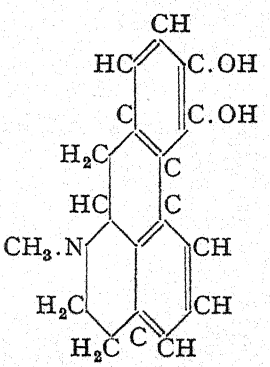
codeinone, obtained by oxidising codeine with chromic acid or potassium permanganate.[1] The changes involved are summarised in the foregoing scheme, in which the heavy type denotes groups taking part in the reactions.

As is apparent from the above formulæ, codeinone is the ketone corresponding to the alcohol codeine. It is also closely related to thebaine, which according to Knorr (*loc. cit.*) is the *methyl ether of the enolic form of codeinone*. In this respect thebaine is related to codeinone in the same way as codeine is to morphine. It was therefore of interest to discover a means of converting thebaine into codeinone and codeinone into thebaine.

The first part of the problem has already been solved in two ways, as indicated above. On the one hand, Knorr succeeded in converting thebaine into codeinone by simple hydrolysis with hot or cold dilute acids, and on the other, Freund observed the formation of codeinone from the bromo-derivative of thebaine.

Eukodal[2] is the hydrochloride of dihydro-hydroxy-codeinone, $C_{18}H_{21}O_4N$, HCl. It is a white powder which melts unsharply at 270°. Like codeine and morphine it is a narcotic, but is more rapid in its action than either of these. It exerts no harmful influence on the heart.

Apomorphine, which has been mentioned on p. 763, is obtained by the action of dehydrating agents on morphine. Physiologically, it has quite different properties from morphine; it is no longer a narcotic, but is an expectorant and emetic. Pschorr[3] has shown that its composition corresponds in all probability to the annexed formula. This structure has recently been confirmed by the synthesis of *dl*-apomorphine dimethyl ether.[4] Apomorphine methobromide is also used therapeutically as an emetic under the name *euporphine*.[5] The latter is less violent in its action than apomorphine; consequently it produces less strain on the heart and may be used for a longer period without danger to the patient.



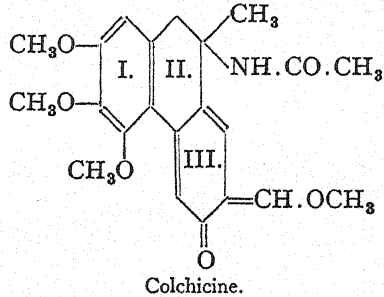
ALKALOIDS OF THE MEADOW SAFFRON

To this group belong colchiceine, $C_{21}H_{23}NO_6 + \frac{1}{2}H_2O$, and colchicine, $C_{22}H_{25}NO_6$. **Colchicine** melts at 143° to 147° and is very poisonous. It is employed medicinally in cases of rheumatism and gout. A. Windaus[6] has shown that the alkaloid is derived from 9-methyl-phenanthrene,

[1] Ach and Knorr, *Ber.*, 1903, **36**, 3067. [2] M. Freund and E. Speyer, *Münch. med. Wochenschr.*, **1927**, 380. E. Merck's *Jahresbericht*, **1916**, 307. [3] Pschorr and collaborators, *Ber.*, 1902, **35**, 4377; 1907, **40**, 1980. [4] Avenarius and Pschorr, *Ber.*, 1929, **62**, 321. E. Späth and O. Hromatka, *ibid.*, p. 325. See, however, Gulland and co-workers, *J. C. S.*, **1929**, 1791, 1666. *Chem. and Ind.*, 1938, 774. [5] *C.*, 1905, **I**, 702; 1906, **I**, 1067. [6] A. Windaus, *Ann.*, 1924, **439**, 59.

and assigns it the following structure, in which the position of substituents in ring III is still uncertain.

Colchicine has a remarkable influence on the growth and heredity of plants when injected into the buds or used as a bath. This treatment



Colchicine.

leads to the appearance of large numbers of new varieties, the characteristics of which are hereditary. Astonishing changes have thus been effected in numerous species.

VIII

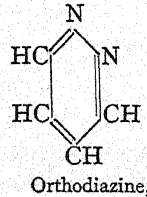
Azines

Under the heading of *azines* are grouped various classes of compounds containing a six-membered ring built up of carbon and two or more atoms of nitrogen, or of carbon and nitrogen together with oxygen or sulphur. Compounds of this type containing oxygen are termed *oxazines* ; those containing sulphur are known as *thiazines*.

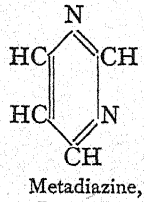
The azines are usually named in accordance with the number of nitrogen atoms in the ring, *e.g.* diazines, triazines, tetrazines, etc. These six-membered rings may be compared with the five-membered azole rings previously described. Belonging to this group are important classes of dye-stuffs.

I.—DIAZINES

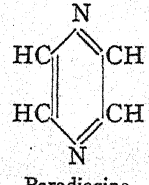
The simplest azines, containing a ring composed of four carbon atoms and two nitrogen atoms, will be taken first. Three series of diazines are theoretically possible, derived from the following compounds :—



Orthodiazine, Pyridazine



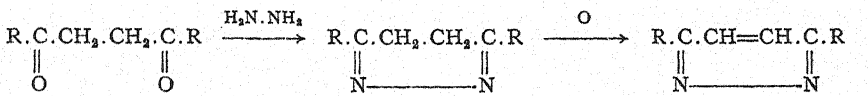
Metadiazine, Pyrimidine



Paradiazine, Pyrazine.

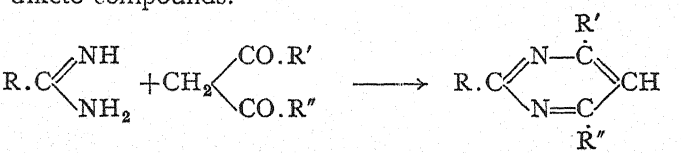
All of these are known.

Orthodiazines or **pyridazines** can often be prepared by the oxidation of their dihydro-derivatives, obtained by the condensation of hydrazines with 1 : 4-diketones or 1 : 4-keto-acids.



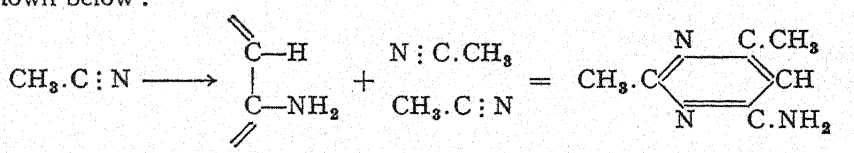
The parent substance, *pyridazine*, results from the action of hydrazine hydrate on the acetin of nitro-succinaldehyde, $O:CH.CH(NO_2).CH:CH.O.CO.CH_3$, fumaraldehyde being formed as an intermediate compound.[1] It is a colourless liquid, b.p. 205° at 755·5 mm. The base has an odour resembling that of pyridine, and the majority of its salts are readily soluble in water.

Metadiazines or **pyrimidines**, which include the cyclic ureides and purines, play an important part in physiological processes. They may be prepared by condensing the amidines of various carboxylic acids with 1 : 3-diketo-compounds.



Amidines, urea and urea derivatives condense with cyano-acetic acid to give substituted pyrimidines containing an amino-group in position 4. These compounds are used in the synthesis of various xanthine bases [2] (see p. 347).

Pyrimidine derivatives are also obtained by the condensation of dicyandiamide, or of guanyl urea, with malonic ester, acetoacetic ester, cyano-acetic ester or their derivatives.[3] The polymerisation products of aliphatic nitriles known as **cyanalkines**,[4] which have been mentioned in an earlier chapter, are also amino-pyrimidines. These are formed under the influence of sodium. It is assumed that two hydrogen atoms in a molecule of nitrile migrate from carbon to nitrogen, and that the resulting complex then unites with two other molecules of nitrile, as shown below :

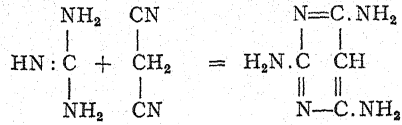


Labile hydrogen is therefore necessary for the formation of a cyanalkine. Hence only primary nitriles (RCH_2CN), which contain two hydrogen atoms attached to the α-carbon atom, can undergo such a change. A mixture of nitriles will react together in this way if at least one of them is of primary character. Tertiary nitriles give compounds of the cyanuric series. This change is brought about even more readily by use of sodamide. It is

[1] R. Marquis, *J. C. S.*, 1903, A, i, 370. See also E. Täuber, *Ber.*, 1895, **28**, 451. S. Gabriel, *Ber.*, 1909, **42**, 654. M. Lange, *Ber.*, 1909, **42**, 576. [2] W. Traube, *Ber.*, 1900, **33**, 1371, 3035 ; 1904, **37**, 2267. [3] *J. C. S.*, 1906, A, i, 705. [4] For further details see E. v. Meyer, *J. C. S.*, 1906, A, i, 411.

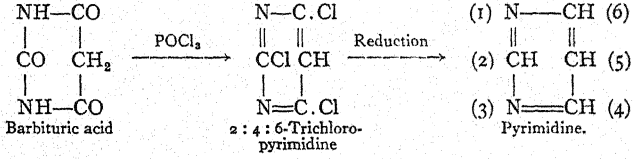
also possible to use sodium methoxide, the reaction being carried out in sealed tubes at a temperature of 130° to 140°.

2 : 4 : 6-*Triamino-pyrimidine* is prepared by the action of malono-nitrile on guanidine, in accordance with the equation [1]



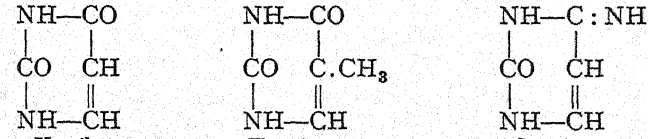
Whereas the pyrimidines are strongly basic in character, the oxypyrimidines possess both basic and phenolic properties.

Pyrimidine, the parent compound of this group, is best prepared from barbituric acid by treatment with phosphorus oxychloride and reduction of the resulting trichloro-derivative.[2]



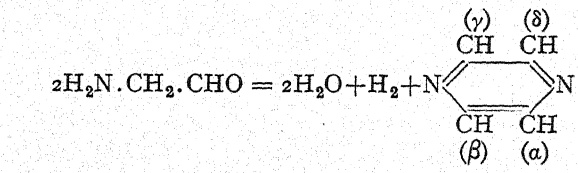
It is a crystalline compound of narcotic odour, and dissolves readily in water. It melts at 21° and boils at 124°.

Derivatives of pyrimidine are of great importance physiologically, and take part in a number of fundamental life processes. For example, they have been shown by Kossel to be present in the cell nucleus, where the synthetic changes associated with the growth of the cell take place. Simple derivatives of pyrimidine which have been isolated from animal and vegetable nucleins (see p. 803) are *uracil*, *thymine* and *cytosine*.



Uracil (2 : 6-Dihydroxy-pyrimidine) — Thymine (5-Methyl-2 : 6-dihydroxy-pyrimidine) — Cytosine

The **paradiazines** or **pyrazines** are prepared by the elimination of water and hydrogen from α-amino-aldehydes or α-amino-ketones, *e.g.*,



As a result of this method of preparation, these compounds are also called **aldines** or **ketines.** They are weak bases, their salts being hydrolysed in aqueous solution. When reduced with sodium and alcohol, pyrazines are converted into the hexahydro-derivatives or **piperazines,** which are analogous to the piperidines.

[1] Traube, *Ber.*, 1904, **37**, 4544. [2] Gabriel, *Ber.*, 1900, **33**, 3666.

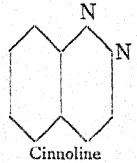
Pyrazine itself is produced by the condensation of amino-acetaldehyde or amino-acetal. It melts at 55°, boils at 115°, and has an odour of heliotrope. Its reduction product, *piperazine*, which is a strong diacid base, has already been described on p. 247. *α : γ-Dimethyl-pyrazine, ketine*, $C_4H_2(CH_3)_2N_2$, is a liquid boiling at 153°. It is obtained from isonitroso-acetone by reduction, amino-acetone being formed as an intermediate product. It may also be prepared by the distillation of glycerol with ammonium salts. The tartrate of αγ-dimethyl-piperazine (obtained by reducing αγ-dimethyl-pyrazine) has been used, under the name of **lycetol,** as a solvent for uric acid in cases of gout. Piperazine has also been employed for the same purpose.

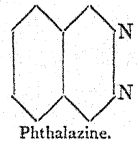
Among other derivatives of piperazine are the 2 : 5-*diketo-piperazines*, described on p. 223. These have been used in the synthesis of polypeptides. Dialkyl-diketo-piperazines have also been synthesised.[1]

II.—BENZO-DIAZINES

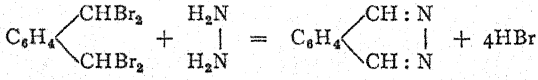
The ring systems described under diazines may also occur in combination with benzene nuclei, thus giving rise to a number of new classes of compounds. These are termed mono-benzo-diazines or dibenzo-diazines, according as one or two benzene nuclei are condensed with the diazine ring.

From pyridazine are derived *cinnolines*[2] and *phthalazines*.

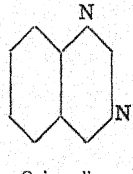

Cinnoline

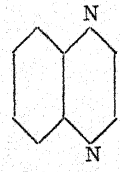

Phthalazine.

Phthalazine is obtained by the action of hydrazine on ortho-derivatives of benzene which are brominated in the side chain.[3]

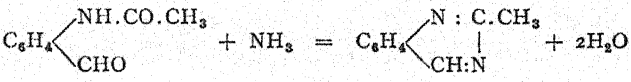


Pyrimidines and pyrazines give rise respectively to quinazolines and quinoxalines.


Quinazoline

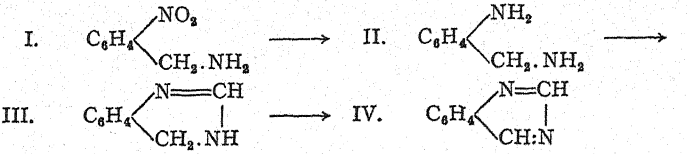

Quinoxaline.

Quinazolines are prepared by the action of ammonia on acyl derivatives of *o*-amino-benzaldehydes.



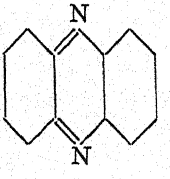
[1] Rosenmund, *Ber.*, 1909, **42**, 4470. [2] See also Busch and Rast, *Ber.*, 1897, **30**, 521. R. Stoermer and H. Fincke, *Ber.*, 1909, **42**, 3115. O. Widmann, *ibid.*, 4216. [3] For other methods see S. Gabriel, *Ber.*, 1903, **36**, 3373.

They are strong bases, which are readily reduced to their dihydro-compounds. *Quinazoline* itself is a solid, m.p. 48° and b.p. 243°. It is obtained from *o*-nitro-benzylamine (I), which is first reduced to *o*-amino-benzylamine (II). The latter is then treated with formic acid, and the dihydro-quinazoline (III) so obtained is oxidised to quinazoline [1] (IV).

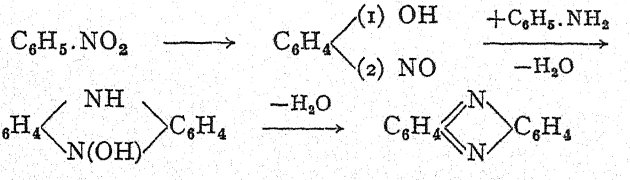


The preparation of **quinoxalines** by the condensation of *o*-diamines with 1 : 2-diketones has been mentioned on pp. 255 and 396. These are weakly basic compounds, which may be reduced to hydro-quinoxalines, but are stable towards oxidising agents.

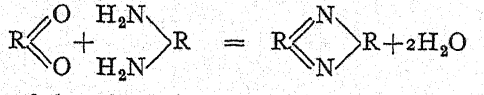
In the dibenzo-diazine series the most interesting compounds are the **dibenzo-paradiazines** or **phenazines.** Several important classes of dye-stuffs, such as the eurhodines, indulines and safranines, belong to this group.

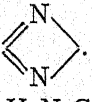


The simplest example is *phenazine*, which may be represented by the annexed formula. **Phenazine** crystallises in bright yellow needles, m.p. 171°, and is easily sublimed. It may be prepared in several ways, *e.g.*, by heating nitrobenzene with aniline [2] at 140°, in the presence of sodium hydroxide. This reaction is probably to be represented as follows :



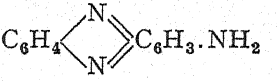
Phenazine may also be synthesised by heating a mixture of catechol and *o*-phenylene diamine. In general, phenazines are formed by the action of *o*-diamines on *o*-quinones.

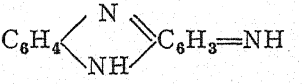


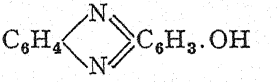
The majority of the phenazines are yellow, weakly basic compounds, which distil unchanged. Their colour is due to the presence of the chromophore group  . Simple azines, such as phenazine, tolu-phenazine, $CH_3.C_6H_3N_2C_6H_4$, naphtho-phenazine,[3] $C_{10}H_6N_2C_6H_4$, naphthazine, $C_{10}H_6N_2C_{10}H_6$, phenanthra-phenazine, $C_{14}H_8N_2C_6H_4$, and anthrazine, $C_{14}H_8N_2C_{14}H_8$, are not in themselves dye-stuffs. But they become so on the entrance of amino or hydroxyl groups into the molecule.

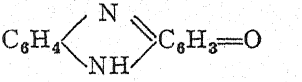
[1] Gabriel and Colman, *Ber.*, 1904, **37**, 3643. [2] Wohl and Aue, *Ber.*, 1901, **34**, 2442. [3] $\alpha\beta$-Naphtho-phenazine is obtained by the condensation of α-nitroso-β-naphthol with *o*-phenylene diamine. F. Ullmann and R. Heisler, *Ber.*, 1909, **42**, 4263.

Before proceeding further, it should be mentioned that, in addition to the usual formulæ of types I and II for the amino- and hydroxy-phenazines, the para-quinonoid formulæ I*a* and II*a* have certain advantages, although the basic properties of the amino-compounds and the phenolic properties of the hydroxyl compounds support I and II.

Amino-phenazine I. 

or I*a*. 

Hydroxy-phenazine II. 

or II*a*. 

Careful consideration of all the facts has led to the conclusion that these compounds are probably tautomeric, each reacting in the two forms indicated. A few of the more important dyes belonging to this series are described in the following pages.

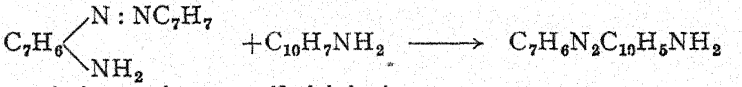
1. Eurhodines or Aminophenazines [1]

The eurhodines may be prepared by the following general methods :

1. By the condensation of quinones with triamines containing two amino-groups in the ortho-position to one another, or by the condensation of amino-quinones with ortho-diamines. (Compare phenazine, p. 776.)

2. By the action of nitroso-dimethylaniline, or of quinone dichloro-di-imines (see p. 434), on certain monamines which are substituted in the para-position.

3. By the action of *o*-aminoazo-compounds on monamines. It was in this way that Witt obtained the first eurhodine, by heating *o*-amino-azo-*p*-toluene with α-naphthylamine.



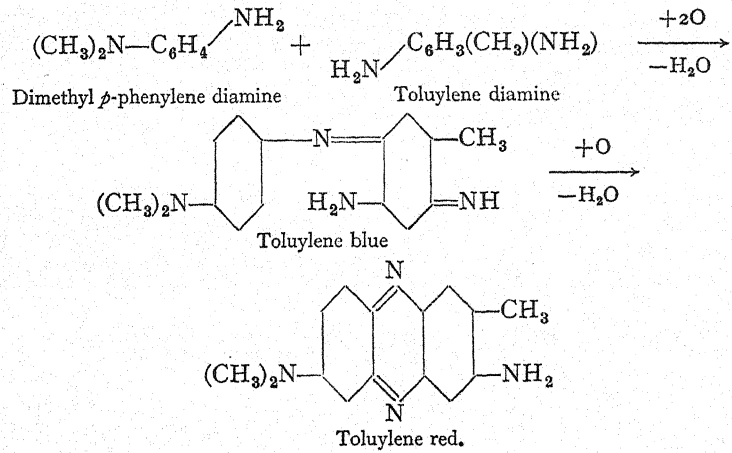
o-Amino-azotoluene α-Naphthylamine.

The simplest eurhodines are weakly basic dye-stuffs, giving monacid salts which dye silk a red colour. As, however, the salts are dissociated in water, this red colour is changed into the yellow of the base on washing.

Toluylene red is formed by oxidising a mixture of dimethyl-*p*-phenylene diamine and *m*-toluylene diamine at the boiling-point. *Toluylene blue*, an indamine derivative, occurs as an intermediate product and is converted into toluylene red by elimination of hydrogen.

[1] O. Witt, the discoverer of the eurhodines, only applied this name to the monamino-azines. At the present time the term is used generally to include all amino-azines.

Toluylene red crystallises in orange-red needles, dyes silk and tannin-mordanted cotton a scarlet red, and is used commercially under the name of " neutral red."



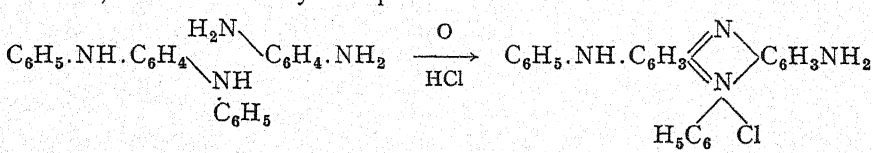
2. Eurhodols or Hydroxyphenazines

These are obtained by the action of concentrated hydrochloric acid on eurhodines at 180°, and also by the fusion of phenazine sulphonic acids with potassium hydroxide. In their dyeing properties they resemble the eurhodines, but differ in having both basic and phenolic properties.

3. Safranines, Aposafranines and Indulines

The safranines are diamino-azines containing at least three hydrocarbon nuclei. They are strongly basic crystalline compounds, which are readily soluble in water and dye yellowish red to violet colours. They may be prepared by the following reactions :—

1. By the oxidation of a mixture of a *m*-amino-diphenylamine and a *p*-diamine. In the case of diphenyl-*m*-phenylene diamine and *p*-phenylene diamine, the reaction may be represented as follows :

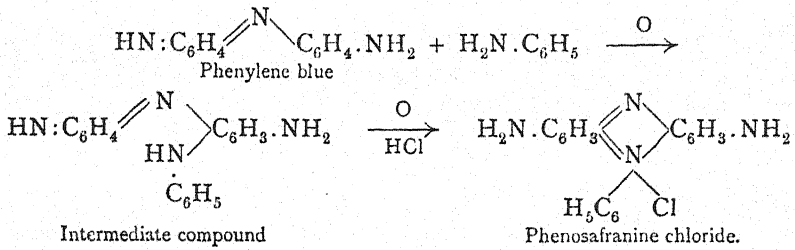


2. By the oxidation of a mixture of a *p*-diamino-diphenylamine, or of an indamine, with a primary monamine.[1]

The safranines form three series of salts, monacid (red), diacid (blue) and triacid (green). Only the monacid salts are stable towards water, the others are decomposed by it. Animal fibres, as well as tannin-mordanted cotton, are dyed red by the safranines. Both of the amino-groups in these compounds may be diazotised.

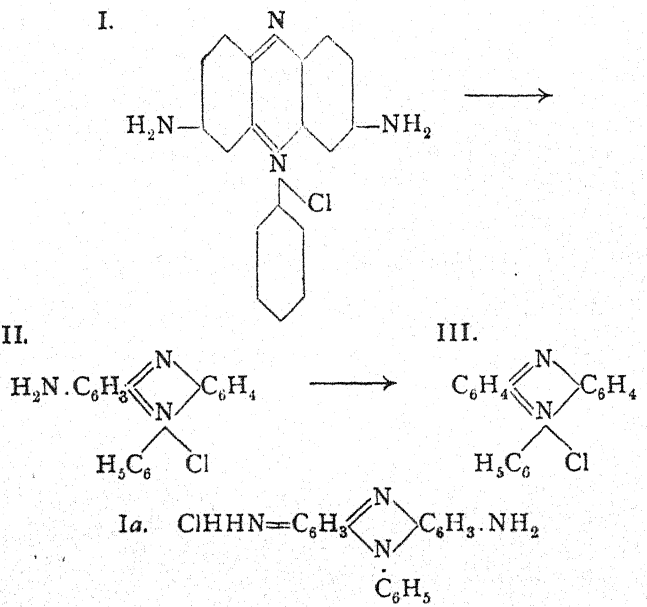
[1] Nietzki, *Ber.*, 1883, **16**, 464; 1886, **19**, 3163. Hardin, *Ber.*, 1900, **33**, 1212.

The *constitution of the safranines* has been solved by the work of Nietzki [1] and Kehrmann. **Phenosafranine,** the simplest member of the



Intermediate compound — Phenosafranine chloride.

the group, has been shown to be the phenyl-ammonium derivative of symmetrical diamino-phenazine. Its hydrochloride is represented as in formula I. When the diazonium compound of this base is heated with alcohol, one amino-group is eliminated and **aposafranine** (II) is formed. In a similar manner the diazonium derivative from the latter may be converted into phenyl-phenazonium chloride (III).



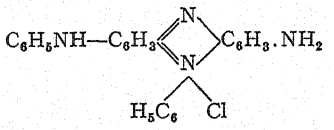
Formula I*a* was proposed for safranine on the ground that the amino-groups could be eliminated from its molecule separately. It appears probable that the compound may react in either of the above forms according to the nature of the reaction.

The safranine of commerce consists chiefly of **tolusafranine,** $C_{21}H_{20}N_4HCl$. It is prepared by oxidising a mixture of one molecule of *p*-toluylene diamine and two molecules of *o*-toluidine by means of potassium bichromate or manganese dioxide. *p*-Toluylene diamine, $C_6H_3(CH_3)(NH_2)_2$, is obtained by the reduction of amino-azotoluene,

[1] Nietzki, *Ber.*, 1896, 29, 1442. Kehrmann, *ibid.*, 2316; *Helv. Chim. Acta*, 1921, 4, 39, 521.

which in turn is prepared from *o*-toluidine. Safranine dyes tannin-mordanted cotton a scarlet red and silk a fine rose tint, but these shades are not fast to light.

Mauveine, the first aniline dye-stuff to be prepared industrially, is of great historical interest. It was obtained by Perkin in 1856, by the oxidation of crude aniline, and consists of a mixture of phenylated safranine,

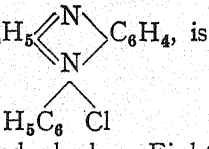


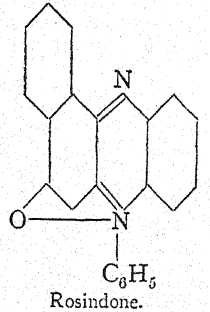
and its homologues.

Magdala red, $C_{30}H_{21}N_4Cl$, was at one time extensively used. It is a safranine of the naphthalene series.

Aposafranines

Aposafranine, which is formed by the elimination of one amino-group from phenosafranine (see p. 779), is a typical member of a comparatively large group of dyes. In this group are now included many compounds formerly classed as indulines, such as the rosindulines and iso-rosindulines, both of which contain a naphthalene nucleus. In the *rosindulines* the amino-group is present in the naphthalene nucleus, and in the *iso-rosindulines* in the benzene nucleus (O. Fischer and Hepp).

Rosinduline is prepared by heating benzene-azo-α-naphthylamine with aniline and alcohol under pressure, and also by other methods. Its hydrochloride,  , is a red dye. The disulphonic acid dyes a yellowish red shade. Eighteen structural isomerides of rosinduline are known, in which the amino-group occupies different positions in the naphthalene, benzene, or N-phenyl nucleus.[1]



Rosindone.

Phenyl-rosinduline, a derivative in which the amino-group of rosinduline is phenylated, is obtained by heating benzene-azo-α-naphthylamine with aniline and aniline hydrochloride. Its disulphonic acid is

[1] Kehrmann and collaborators, *Ber.*, 1897, **30**, 2632; 1898, **31**, 3097; 1899, **32**, 927, 2627; 1900, **33**, 1543, 3276; 1901, **34**, 1225, 3092; *Ann.*, 1896, **290**, 275. *Helv. Chim. Acta*, 1925, **8**, 655.

used commercially as a red dye-stuff for wool, under the name of **azocarmine.**

When safranines and aposafranines are heated with alkali or concentrated hydrochloric acid the amino-groups are replaced by hydroxyl groups. The reaction is accompanied by a simultaneous isomerisation into the *p*-quinonoid or internal salt structure, and leads to the formation of safranols, safranones and rosindones.

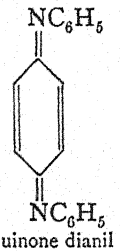
Rosindone is obtained in this way by heating rosinduline with concentrated hydrochloric acid.

Rosinduline G is a sulphonic acid of rosindone, and is used as a red acid dye.

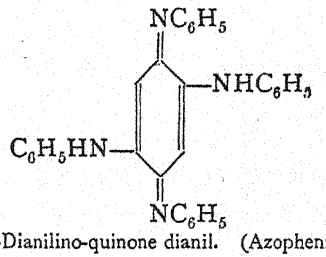
Indulines

The indulines, the first example of which was prepared in 1863 by Dale and Caro, give shades resembling those of indigo blue. They occur as by-products in the " magenta melt," and are prepared by heating aminoazo-benzene with primary aromatic amines and their salts (induline melt).

Induline, $C_{30}H_{23}N_5$, is prepared by heating aminoazo-benzene with aniline hydrochloride (Dale and Caro, 1863). The intermediate com-



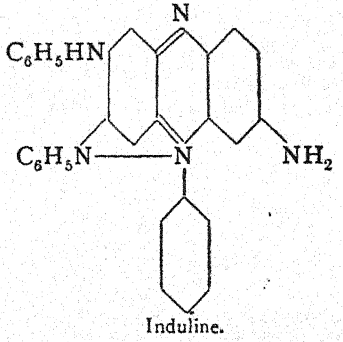
Quinone dianil



2 : 5-Dianilino-quinone dianil. (Azophenine.)

pounds in this reaction have been shown to be quinone dianil and 2 : 5-dianilino-quinone dianil, or *azophenine.*

O. Fischer and Hepp have proved that induline has the annexed formula.



Induline.

Some of the most important indulines have been synthesised by Kehrmann.[1]

Induline gives reddish violet salts which are soluble in water, and are used directly on tannin-mordanted cotton.

On heating the dye with aniline and aniline hydrochloride, more phenyl and amino-phenyl groups enter the molecule, with the formation of complex indulines. These are insoluble in water and are used either in alcoholic solution (spirit indulines), or in the form of their water-soluble sulphonic acids, for dyeing wool. Cotton may be dyed with the aid of *acetin*, a mixture of glyceryl esters of acetic acid,

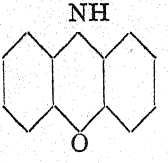
[1] F. Kehrmann, *Ber.*, 1923, 56, 2394.

which acts as a solvent. For this purpose, induline is made into a paste with tannin and acetin, and printed on to the material. The acetin dissolves the dye and ensures the formation of the tannin lake. On subsequent treatment with steam the acetin is hydrolysed to glycerol and acetic acid and the lake is deposited on the fibres.

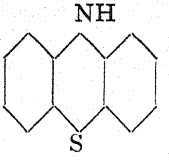
Aniline black is a very valuable dye which is formed when aniline is oxidised by various reagents (such as sodium and potassium chlorates in presence of copper and vanadium compounds). It is always produced directly on the fibre and is widely employed in calico-printing and cotton-dyeing, but is not much used for wool. It is an amorphous, violet-black powder, which is insoluble in water and alcohol, is strongly basic and forms green, unstable salts with acids. The constitution of aniline black is still unknown. Its composition is probably represented by $C_{30}H_{27}N_5$.

III.—OXAZINE (AZOXINE) AND THIAZINE (THIONINE) DYES[1]

These compounds contain a nucleus built up of four carbon atoms, a nitrogen atom, and, according as they are derived from phenoxazine or phenthiazine, an atom of oxygen or sulphur.



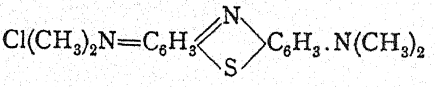
Phenoxazine

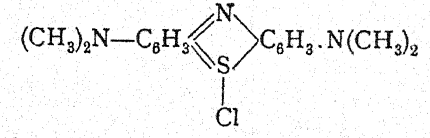


Phenthiazine,
Thio-diphenylamine.

The amino and hydroxy derivatives of these parent substances are leuco-compounds, which on oxidation give the corresponding dyes. *Phenoxazine* crystallises in plates, m.p. 148°, and is prepared by fusing *o*-amino-phenol with catechol.

Two suggestions have been put forward as to the constitution of dyes of this class containing an ammonium grouping. The older view of Bernthsen, O. Fischer and others, which is adopted here, is that they are quinonoid ammonium salts.[2] Kehrmann, however, regards them as oxonium and thionium salts. The two types of formulæ may be illustrated in the case of *methylene blue*.

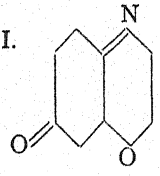
I. Ammonium formula 

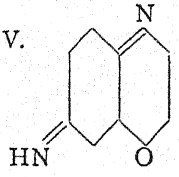
II. Thionium formula 

With regard to the nomenclature of these compounds, all dye-stuffs containing the complex III, such as gallocyanin, are grouped together under the name of *oxazones*. Other dyes, such as Capri blue, contain

[1] Kehrmann, *Ann.*, 1902, **322**, 1; *Ber.*, 1906, **39**, 914. A. Hantzsch, *Ber.*, 1905, **38**, 2143; 1906, **39**, 153, 1365. [2] A. Bernthsen, *Ch. Zeit.*, 1908, **32**, 956.

a quinone-imine structure (IV), and are known as *oxazimes*. The corresponding sulphur derivatives are termed *thiazones* and *thiazimes*.

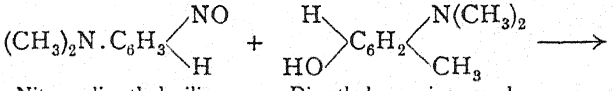
III. 

IV. 

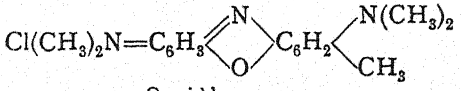
The chromophore present in such compounds is not the oxazine or thiazine ring, as is sometimes assumed, but the paraquinonoid grouping.

These dye-stuffs are prepared by the condensation of nitroso-dimethylaniline, nitroso-phenols, or quinone dichloro-imines with tertiary amino-phenols or polyhydric phenols.[1]

In this way the dye **Capri blue** is obtained by the interaction of nitroso-dimethylaniline and dimethyl-*m*-amino-cresol.

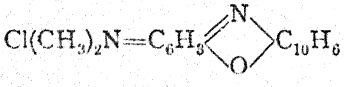


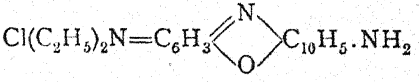
Nitroso-dimethylaniline Dimethyl-*m*-amino-cresol.



Capri blue.

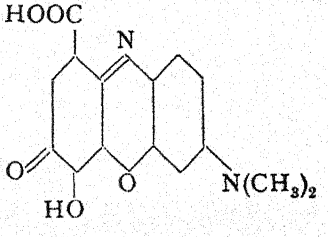
Meldola's blue (*naphthol blue*, *new blue R*, *fast blue*), which dyes tannin-mordanted cotton a violet blue shade, is prepared by the action of nitroso-dimethylaniline on β-naphthol. Its constitution is represented by formula V.

V. 

VI. 

Nile blue, formula VI, is prepared by the action of nitroso-diethyl-*m*-aminophenol on α-naphthylamine. It dyes silk and tannin-mordanted cotton a greenish blue shade.

Gallocyanin is formed by the action of nitroso-dimethylaniline on gallic acid. It is a carboxylic acid of the annexed formula.



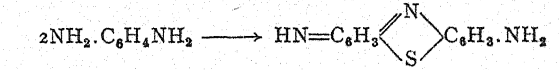
Gallocyanin is a mordant dye, which gives a fine blue-violet lake with chromium oxide. It is largely used in calico printing.

On heating gallocyanin with aniline the carboxyl group is replaced by the group —NHC_6H_5. When the latter is sulphonated by heating the compound with concentrated sulphuric acid, a sulphonic acid is obtained which is used commercially under the name of *Delphine blue*.

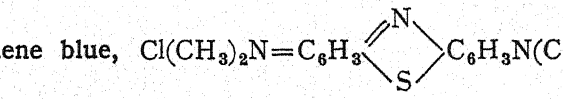
[1] See also A. Fairbourne and H. Toms, *J. C. S.*, 1921, **119**, 2076.

Phenthiazine, *thio-diphenylamine* (see p. 782), is also the parent compound of a number of dye-stuffs. It melts at 150°, boils at 370°, and is prepared in an analogous manner to phenoxazine by heating *o*-amino-thiophenol with catechol, or more conveniently by heating diphenylamine with sulphur or sulphur chloride. The introduction of amino-groups into phenthiazine leads to the formation of leuco-compounds, which on oxidation yield dyes. These were first prepared by Lauth by the oxidation of *p*-diamines in the presence of hydrogen sulphide. *Methylene blue* is the most important member of this group.

Lauth's violet, *thionine, amino-phenthiazine,* is prepared by oxidising *p*-phenylene diamine hydrochloride in a solution containing hydrogen sulphide.



The aqueous solution of its hydrochloride is violet in colour.

Methylene blue,  , was discovered in 1876 by Caro, who obtained it by oxidising dimethyl-*p*-phenylene diamine in presence of hydrogen sulphide. It may be prepared on a large scale by the reduction of *p*-nitroso-dimethylaniline with hydrogen sulphide in strongly acid solution, followed by oxidation of the resulting amino compound with ferric chloride in the presence of hydrogen sulphide. During this reaction one atom of sulphur enters into combination with two molecules of the amino compound, and one atom of nitrogen is eliminated as ammonia. In modern practice the sulphur is introduced by means of sodium thiosulphate. The oxidation of dimethyl-*p*-phenylene diamine, in the presence of sodium thiosulphate, results in the formation of the thiosulphonic acid of the base, $C_6H_3[N(CH_3)_2](NH_2)(S.SO_3H)$. The latter, on being mixed with dimethylaniline and subjected to further oxidation, yields the corresponding indamine thiosulphonic acid, which when boiled with dilute acid parts with sulphuric acid to give methylene blue.[1]

The dye is precipitated from aqueous solution by the addition of zinc chloride and common salt, and is placed on the market in the form of its zinc chloride double salt. The latter is very soluble in water. It does not dye wool readily but is used for silk and tannin-mordanted cotton, the colour being very fast to light. It is the most important of all the blue basic dyes, and is widely used in calico-printing and cotton-dyeing.

Methylene azure is produced by the oxidation of methylene blue in dilute acid solution (*e.g.* potassium dichromate and sulphuric acid), when the N-methyl groups are partially replaced by hydrogen.[2]

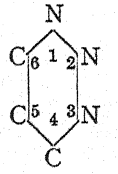
When treated with nitrous or nitric acid, methylene blue yields a

[1] Bernthsen, *Ann.*, 1885, **230**, 73; 1889, **251**, 1. [2] Kehrmann, *Ber.*, 1906, **39**, 1405. Bernthsen, *ibid.*, 1804.

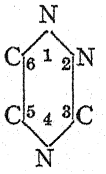
dark green colouring matter which is probably a mononitro-derivative of methylene blue. This is known as **methylene green** and dyes a dark green colour.

IV.—TRIAZINES

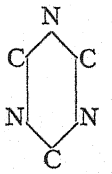
Three different six-membered rings composed of three nitrogen and three carbon atoms are theoretically possible. Derivatives of all three types are known.



Vicinal triazines, β-triazines

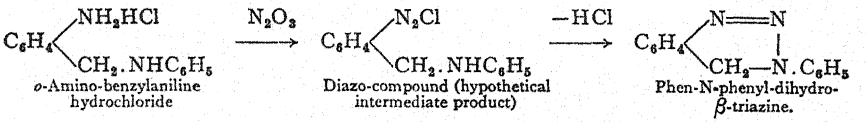


Asym. triazines, α-triazines

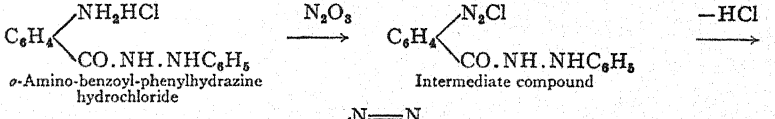


Sym. triazines, cyanidines.

Derivatives of vicinal or β-triazine are prepared by the action of nitrous acid on *o*-amino-benzylamine bases,[1] or on *o*-amino-benzoyl phenylhydrazine,[2] a reaction which probably results in the intermediate formation of diazo-compounds, *e.g.*,

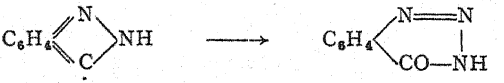


o-Amino-benzylaniline hydrochloride — Diazo-compound (hypothetical intermediate product) — Phen-N-phenyl-dihydro-β-triazine.



o-Amino-benzoyl-phenylhydrazine hydrochloride — Intermediate compound — Phen-N-phenylamino-β-triazone.

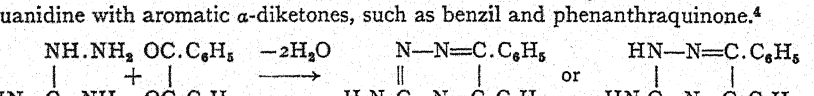
Benzazimide, a member of this series, is formed by the action of nitrous acid on the



3-Amino-indazole — Benzazimide.

amide of anthranilic acid, and also by the oxidation of 3-amino-indazole, as the result of ring extension.[3]

Derivatives of asymmetrical or α-triazine are obtained by the condensation of amino-guanidine with aromatic α-diketones, such as benzil and phenanthraquinone.[4]

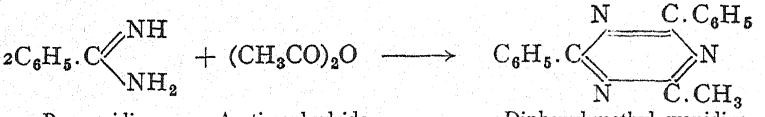


Amino-guanidine — Benzil — 3-Amino-5 : 6-diphenyl-α-triazine.

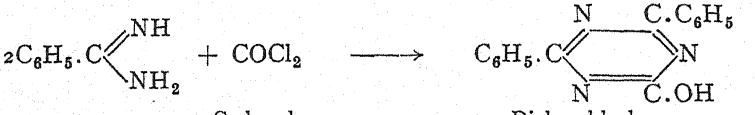
It has not yet been decided whether the amino- or the imino-formula best represents the constitution of these compounds. Probably the systems are tautomeric. They have very little basic character and are not affected by nitrous acid. Potassium hydroxide converts diphenyl-aminotriazine into diphenyl-hydroxytriazine.

[1] M. Busch, *Ber.*, 1892, **25**, 445. [2] König and Reissert, *Ber.*, 1899, **32**, 782. [3] Bamberger, *Ann.*, 1899, **305**, 289. [4] Thiele and Bihan, *Ann.*, 1898, **302**, 299.

The polymeric cyanic compounds, such as cyanuric acid, cyamelide and melanine, are interesting derivatives of **symmetrical triazine** or **cyanidine.** These have already been discussed on pp. 331 *et seq.*



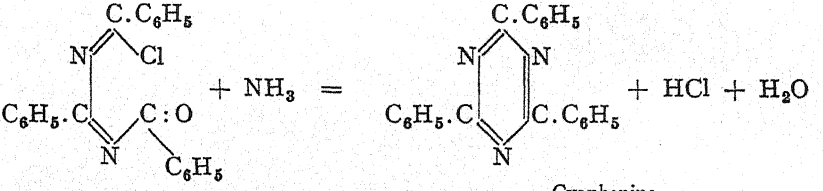
Benzamidine — Acetic anhydride — Diphenyl-methyl-cyanidine



Carbonyl chloride — Diphenyl-hydroxy-cyanidine.

A general method of preparing the **cyanidines** is by the action of acid anhydrides, or of carbonyl chloride, on aromatic amidines.[1]

Many cyanidines may be obtained by the action of aluminium chloride on a mixture of benzonitrile and benzoyl chloride or a fatty acid chloride.[2] In the reaction between benzonitrile and benzoyl chloride it is advantageous to add ammonium chloride to the mixture, when cyaphenine or triphenyl cyanidine is produced in moderately good yield. This is one of the earliest known cyanidines. The reaction is probably due to the initial formation of a condensation product of benzonitrile and benzoyl chloride, which then interacts with ammonia in the following manner :

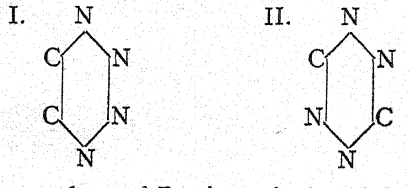


Cyaphenine.

Cyaphenine crystallises in colourless needles which melt at 233°, and readily sublime. Its constitution follows from its formation by the action of sodium on a mixture of cyanuric chloride and bromo-benzene. It has no basic properties, and is decomposed by nascent hydrogen into ammonia and lophine (2 : 4 : 5-triphenyl-glyoxaline).

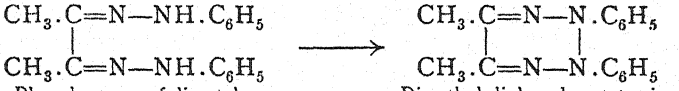
V.—TETRAZINES

Two isomeric series of tetrazines are known, derived from the following ring systems :



[1] Pinner, *Ber.*, 1892, **25**, 1624. [2] For the mechanism of the reaction see Eitner and Krafft, *Ber.*, 1892, **25**, 2263.

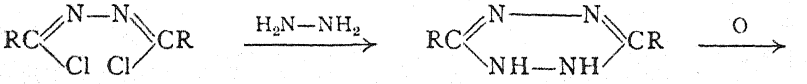
The ring system (I) is present in the **osotetrazines,** obtained by oxidising the osazones (see p. 255) formed by the union of 1 : 2-diketones with hydrazines.[1]



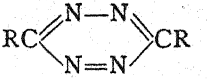
Phenylosazone of diacetyl — Dimethyl-diphenyl-osotetrazine.

The osotetrazines are colourless neutral compounds which crystallise well. On reduction they are again converted into osazones. When osotetrazines are warmed with mineral acids the ring contracts with the formation of osotriazoles (see p. 666). An open-chain structure is also under consideration for these compounds.[2]

Symmetrical tetrazines containing the ring system (II) are readily prepared by the oxidation of dihydro-tetrazines, which result from the action of hydrazine on imino-ethers,[3] or on dichlorides of diacidyl hydrazides.[4] Dihydro-tetrazines can also be obtained from diazoacetic ester.[5]



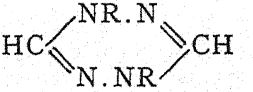
Diacidyl hydrazide dichlorides — Dihydro-tetrazines.



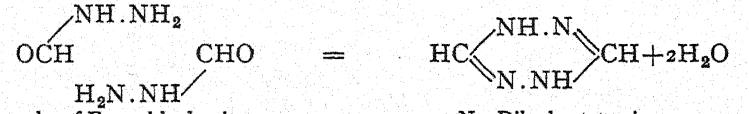
Sym. tetrazines.

The symmetrical tetrazines have a deep red colour. They are stable towards acids but are decomposed by alkalis.

Bis-hexahydro-tetrazine HN.CH_2.N.CH_2.NH / HN.CH_2.N.CH_2.NH is readily prepared from an aqueous solution of formaldehyde and hydrazine hydrate. It is used in analytical chemistry as a reducing agent.[6]

Compounds having a ring structure of the type 

are described as N,*s-dihydro-tetrazines* or *isodihydro-tetrazines*. The parent compound, **N,*s*-dihydro-tetrazine** or isodihydro-tetrazine, is prepared synthetically by heating formyl-hydrazine at 150° to 200°, and



2 mols. of Formyl-hydrazine — N,*s*-Dihydro-tetrazine.

also from the polymerisation products of diazo-acetic ester (p. 225).

[1] R. Stollé, *Ber.*, 1926, **59**, 1743. [2] D. Vorländer, *Ber.*, 1927, **60**, 849. [3] Pinner, *Ann.*, 1897, **297**, 238. [4] R. Stollé, *J. pr. Ch.*, 1906, [2], **73**, 277. [5] Curtius, Darapsky and E. Müller, *Ber.*, 1908, **41**, 3161; 1909, **42**, 3284. [6] K. A. Hofmann and D. Storm, *Ber.*, 1912, **45**, 1725.

These interesting polymerisation products, which are themselves tetrazine derivatives, have been extensively investigated by Hantzsch and Silberrad.[1]

N,*s*-Dihydro-tetrazine and its derivatives behave as weak monacid bases, the C-dimethyl and diethyl compounds being more basic than the unsubstituted product.[2] The ring is readily ruptured with the production of hydrazines.

IX

Proteins[3]

From the investigations of Emil Fischer, proteins may be defined as naturally occurring substances of high molecular weight, which are largely composed of amino-acid residues united together by an amide type of linking. Other types of units and other modes of union may also be present (see p. 808).

These substances are of great biological interest, since they include some of the most important constituents of the living cell. So intimately are they bound up with the processes of life, that each type of organism, and each kind of cell within the organism, possesses its own characteristic proteins. In fact, in the higher organisms, foreign proteins often act as strong poisons when introduced directly into the blood-stream, instead of by way of the intestinal canal. On these phenomena are based the serological methods of modern medicine. Such reactions of the organism provide a much more sensitive means of identifying individual proteins than any chemical method. In addition, it may be noted that the physico-chemical state in which the protein is present has a great influence on the activity of the cell.

A certain amount of the protein in living organisms is continually being used up in vital processes (*e.g.* gland secretions), and it is necessary for the loss to be replaced. For this purpose plants utilise inorganic nitrates as their main source of nitrogen. The animal body is incapable of building up all the requisite constituents of protein molecules from nitrates and non-nitrogenous organic substances, such as carbohydrates and fats, and consequently makes use of ingested protein to replace the loss. Protein is therefore an essential constituent of animal diet. At one time it was considered that proteins were, in themselves, sufficient to maintain life, and that the most satisfactory and economical diet was one

[1] *Ber.*, 1900, **33**, 58. [2] Hantzsch and Silberrad, *loc. cit.* Dedichen, *Ber.*, 1903, **36**, 1831.
[3] For further information reference may be made to the following sources:—*The Chemical Constitution of the Proteins*, Parts I and II, by R. H. A. Plimmer (Longmans); *The Vegetable Proteins*, by T. B. Osborne (Longmans, 1924); *The General Character of the Proteins*, by S. B. Schryver (Longmans); *Colloid Chemistry of the Proteins*, by Pauli, translated by Thorne (Churchill, 1922); *Chemie der Eiweisskörper*, by O. Cohnheim (Vieweg, Braunschweig); "Untersuchungen über Aminosäuren, Polypeptide und Proteine," by E. Fischer, *Ber.*, 1906, **39**, 530. Sörensen, *J. C. S.*, **1926**, 2995.

containing the highest possible proportion of protein. This has been disproved, however, by recent investigations on nutrition. Moreover, different proteins are not utilised by the organism to the same extent.[1] The older method of regarding the problems of nutrition, as being primarily dependent on the energy content of the food, had therefore to be modified, and more attention paid to the chemical nature of the diet.

At the outset it should be emphasised that the chemical investigation of the proteins is attended with very great difficulty. This is due, on the one hand, to the complexity of the protein molecule, and on the other, to the fact that the usual methods of isolation fail to give pure homogeneous compounds. The chief criterion of the purity and uniformity of a solid substance is its power of crystallisation. As will be seen later, this test can only be applied to the proteins in a very limited sense. The usual method of purifying a liquid compound is by distillation, but no protein can be distilled without decomposition. Hence the study of their physico-chemical properties is of the highest importance in the chemical and physiological investigation of these compounds.

Proteins are colloids and do not diffuse through animal membranes. This property is used in their purification. They occur in complex mixtures from which they are usually isolated by salting out. Owing to their colloidal nature, the proteins so prepared retain adsorbed crystalloids, especially electrolytes, which are exceedingly difficult to remove. After months of dialysis under aseptic conditions, Pauli succeeded in preparing a protein solution practically free from electrolytes. Sörensen,[2] after prolonged dialysis through collodion membranes, was able to obtain protein solutions with reproducible properties, but having a definite, although extremely low, content of ammonium sulphate.

In the properties already described, proteins resemble the *hydrophobe* or *suspensoid colloids* of inorganic chemistry (*e.g.* colloidal metals). In other respects, however, they exhibit differences which led to them being classed with certain other colloids as *hydrophile* or *emulsoid colloids*. Largely through the work of Pauli, Michaelis and Sörensen—and in opposition to the views of Ostwald—this idea has undergone further extension. The properties of natural [3] proteins are not regarded as being explicable solely from the standpoint of colloid chemistry, and the compounds are therefore supposed to occupy an intermediate position between the suspensoids and crystalloids.

The inability of the proteins to diffuse through animal membranes shows that they have a high molecular weight. Nevertheless, protein solutions possess a measurable, though very small, osmotic pressure. Sörensen, who has carried out the most recent and accurate investigations on purified egg albumin, found that the osmotic pressure [4] of the protein

[1] See, for example, Berczeller, *Biochem. Zeitsch.*, 1922, 129, 217. [2] S. P. L. Sörensen and Höyrup, *Z. physiol. Ch.*, 1918, 103, 15. [3] That is, not denatured (see p. 790). [4] It is doubtful whether true values of molecular weight are indicated in such osmotic pressure measurements.

was constant for solutions of a definite composition. This shows that it is possible to reproduce protein solutions containing particles of a definite size.

The addition of alkali salts to a protein solution causes a gradual decrease in the osmotic pressure, and at a definite concentration of the salt the protein is precipitated. During such a precipitation the protein retains its original properties, and, after having been filtered off, may be brought into solution again in its original condition. This method of *reversible precipitation by neutral salts*, which was introduced by Hofmeister, is used for the isolation of certain kinds of proteins. It differs from the precipitation of suspensoid colloids by electrolytes, in that the proteins are only precipitated by a much higher concentration of the salt. As was first shown by Hofmeister, neutral salt precipitation depends on the specific action of the ions of the salt. According to Pauli, cations generally tend to assist and anions to retard precipitation. The relative influence of the ions may be expressed by arranging them in the following "lyotropic" series.[1] The order in which cations assist precipitation is $Li<Na<K<NH_4$, whilst that in which anions retard precipitation is $CNS<I<Br<NO_3<Cl<CH_3COO<HPO_4SO_4$.

In acid media the above order is reversed. It must be remembered, however, that the factors governing precipitation are very complex, and, like most of the laws of protein chemistry so far discovered, the above can only be regarded as a broad generalisation.

It has recently been proved by Pfeiffer that neutral salts affect the solubility of amino-acids in the same way as that of the proteins, and that the alteration in solubility is due to complex salt formation.[2] Hence, during the precipitation of proteins by electrolytes, it is very probable that combination takes place between the neutral salt and the protein.

On the other hand, a precipitation process of a different nature is undergone by protein solutions under the influence of heat, or on addition of certain substances such as alcohol, acetone, solutions of salts of the heavy metals and alkaline earths, etc. For example, when a solution of a protein is heated, the protein becomes coagulated at a definite temperature, which varies with the nature of the protein and the other products present. The insoluble *coagulated protein* is said to be *denatured*, and cannot be reconverted into the original compound. This property is used in removing proteins from a solution, and for their quantitative estimation. Physiological solutions can be freed from protein by means of mercuric chloride and hydrochloric acid (Schenck), and the quantitative estimation of protein is based on its precipitation by alcohol, acetone, tannic acid, or the action of heat.

In the precipitation of proteins by heat it is necessary to distinguish between *denaturation* and the precipitation or *flocculation*[3] *of the*

[1] This lyotropic series has also an important bearing on many biological processes; see Abderhalden's *Lehrbuch*, vol. ii., p. 173 [4th edition]. [2] P. Pfeiffer, *Organische Molekülverbindungen*, p. 106 (Stuttgart, 1922). [3] H. Lüers and M. Landauer, *Z. ang. Ch.*, **1922**, 469. W. C. M. Lewis, *Zeit. Phys. Chem.*, 1927, **130**, 346.

denatured particles. Protein particles which have been denatured by heat possess the properties of suspensoids. While denaturation is a process of unknown character, flocculation is a physico-chemical process and will be more fully discussed.

Coagulation of protein by heat is impeded by strong acids and alkalis, owing to denaturation by the formation of *acid or alkali albuminates*. These albuminates are no longer precipitated on heating. They are insoluble in water or sodium chloride solution, but readily dissolve in dilute acid or alkali. From acid solution they are precipitated by the addition of sodium chloride. In most other respects the acid and alkali albuminates form two quite distinct groups of substances.

The heat coagulation of proteins is also modified by the presence of salts. In general, small quantities of salts retard coagulation, and hence the coagulation temperature (*i.e.*, the lowest temperature at which coagulation takes place) is raised; larger quantities, on the other hand, assist the separation of protein. Consequently, in order to obtain as complete a coagulation as possible under the influence of heat, the protein solution is usually treated with neutral salts. Here again, however, the influences at work are of great complexity.

The properties of a protein solution depend to a large extent on the concentration of hydrogen ion present, and recent research on these compounds has been largely concerned with this question. Owing to their basic and acidic groups, the proteins, like the amino-acids, are amphoteric electrolytes, and exist in aqueous solution in the form of undissociated molecules, anions and cations. It is assumed that hydrogen ions may be produced not only from the carboxyl groups in the protein molecule but also from other sources, *e.g.* by the enolisation of peptide groups:

$$—CH_2.CO.NH— \longrightarrow —CH_2.C(OH):N—$$

The dissociation constants of these acidic and basic groups are very small, most protein solutions being very slightly acid in character. As might be expected, the addition of small amounts of strong acids or alkalis leads to salt-formation and considerably increases the ionisation. Salts of proteins with weak acids and bases, on the other hand, are hydrolytically dissociated. According to Pauli, proteins are polybasic acids and polyacidic bases, but the valency of the ions is very difficult to determine. A solution of protein and alkali, for example, contains a mixture of protein ions of different valency, which varies with the amount of alkali added. Up to a limiting value, the valency increases with the concentration of alkali. On the basis of Ostwald's valency rule Pauli [1] has estimated from conductivity experiments that casein forms a tervalent and globulin a tetravalent anion.

For ampholytes,[2] it may be shown practically, as well as theoretically,

[1] Pauli, *Biochem. Zeitsch.*, 1922, **127**, 150; see, however, L. van Slyke and A. Bosworth, *Journ. Biol. Chem.*, 1913, **14**, 211, 227. [2] An ampholyte is an amphoteric electrolyte, that is, one which dissociates both as an acid and as a base.

that there is a definite concentration of hydrogen ion at which the number of anions becomes equal to the number of cations. This is known as the *isoelectric point.* Under the influence of an electric field the numerical equivalence of anions and cations is indicated by symmetrical movement to anode and cathode. Since, however, the number of ions is at a minimum at the isoelectric point (see below) the electrical migration is also at a minimum. Each protein has its own characteristic isoelectric point, corresponding, in the cases so far examined, to very faintly acidic solutions.

At the isoelectric point the sum of the ions reaches a minimum as compared to the number of undissociated molecules. Hence, if either strong alkali or acid is added in very small concentrations to a protein solution at the isoelectric point, the dissociation is increased owing to salt-formation.

The faintly acid solution at the isoelectric point represents the optimum condition for the heat coagulation of a large number of proteins (Michaelis). At this point serum globulin is precipitated, even without heating.

It has been suggested by Hardy and Bredig that agglomeration is hindered by the electric charge on the colloid particles, but is promoted by surface tension. At the isoelectric point the charge is at a minimum, and the surface tension therefore gains the upper hand.

Viewed from another standpoint, the excess of undissociated protein molecules present at the isoelectric point also has an influence on precipitation. According to Pauli, the ions of a protein differ from the undissociated molecules in their behaviour; they are heavily hydrated, *i.e.*, they are combined with molecules of water, which they lose when they pass back into undissociated molecules. It is very probable that this process is directly concerned in solubility changes. The strong hydration of protein ions, as compared with neutral molecules, is confirmed by the fact that the increased dissociation resulting from the addition of acids or alkalis to a protein solution is accompanied by a marked increase in viscosity. Consequently, at the isoelectric point the number of hydrated ions and the inner friction of the solution are both at a minimum.

In a similar way, other physical properties of protein solutions are dependent on the state of ionisation. For example, ionised protein is more strongly laevorotatory than neutral protein.

All these facts indicate that the electrical condition of the protein particles, unlike that of other colloids, can be largely explained on the basis of the dissociation theory. No distinct boundary line can therefore be drawn between solutions of crystalloid electrolytes and protein solutions, and the reactions of proteins are thus to a large extent true chemical reactions.

The presence of proteins in a solution modifies the properties of other dissolved substances, owing to adsorption, hydration, etc. In some cases proteins prevent the deposition of difficultly soluble salts from solution. This fact is of great biological importance and accounts for the existence of dissolved calcium salts in the body fluids. On the other hand, the

presence of proteins lowers the solubility of many easily soluble salts. Proteins are also efficient protective colloids; in minute amounts they protect suspensoids from precipitation by electrolytes. The number of milligrammes of a protein, which is just insufficient to protect 10 c.c. of a standard colloidal gold solution from precipitation by 1 c.c. of a 10 per cent. solution of sodium chloride, is known as the *gold number* of the protein concerned (Zsigmondy[1]). This number is characteristic for each individual protein.

Crystallisation of Proteins.—The inability of proteins to diffuse through membranes is in strong contrast to the ease of diffusion of crystalloids, and led at first to the conclusion that proteins could not be obtained in a crystalline condition. This was later proved to be incorrect. On the one hand, protein crystals have been found as such in nature, as in the aleurone grains which are widely distributed in the seeds of plants; and, on the other hand, a number of proteins which do not naturally occur in the crystalline state have been converted into this form. For example, crystalline egg albumin was obtained by Hofmeister,[2] and horse serum albumin, hæmoglobin, and globulins from plant seeds have also been prepared in the crystalline condition.

From the work of Sörensen[3] it appears that the crystallisation of proteins in no way differs from that of crystalloids. But, despite this similarity, it is not possible by recrystallisation to purify them to the same extent as other organic compounds, owing to their sponge-like capacity for absorbing impurities from solution.[4]

Although various proteins have been found in the crystalline state in animals and plants, or have been converted into the crystalline form by artificial means, none of these compounds can be regarded as chemically pure. In all probability no protein has yet been obtained in a homogeneous condition.

For this reason, some degree of uncertainty is attached to all investigations so far carried out in protein chemistry, and more especially to molecular weight determinations.[5]

Molecular Weight Determinations.—Among the usual physico-chemical methods employed for the *estimation of molecular weights*, the ebullioscopic method cannot be used owing to the changes undergone by proteins under the influence of heat. The values hitherto obtained by the cryoscopic method are remarkably small,[6] *e.g.* for silk fibroin about 350, a phenomenon for which no satisfactory explantion has yet been advanced.

Sörensen,[7] as a result of careful direct *osmotic pressure measurements*, estimates the molecular weight of crystalline egg albumin at 34,000; and Pauli,[8] from determinations of the valency of the ions of casein and

[1] F. N. Schulz and Zsigmondy, Hofmeister Beiträge, 1902, **3**, 137. [2] F. Hofmeister, *Z. physiol. Ch.*, 1889, **14**, 165; 1891, **16**, 187. [3] Sörensen and M. Höyrup, *Z. physiol. Ch.*, 1918, **103**, 15. [4] Compare Wichmann, *Z. physiol. Ch.*, 1897, **27**, 584; see also Kossel, *Ber.*, 1901, **34**, 3229, 3231. [5] F. N. Schulz, *Die Grösse des Eiweissmolecüls*, Jena 1903. [6] R. O. Herzog and M. Kobel, *Z. physiol. Chem.*, 1924, **134**, 296. [7] Sörensen and Höyrup, *Z. physiol. Ch.*, 1918, **106**, 1. [8] W. Pauli, *Biochem. Zeitsch.*, 1922, **127**, 150.

globulin, has calculated that these two proteins have molecular weights of about 3000 and 12,000 respectively.

Minimum values for the molecular weights of various proteins have been calculated from their *sulphur content*, as determined by elementary analysis. By simple computation it is easily shown that for a sulphur content of 1 per cent. the molecular weight of the protein must be at least 3200. The following figures may be taken as examples of such estimations :

	Per cent. of S	Mol. wt. (assuming 1 atom S to each mol. protein).
Edestin (crystallised) . . .	0·87	3680
Oxyhæmoglobin (horse) . . .	0·43	7440
Egg albumin (crystallised) . .	1·3	2460

In this manner it is possible to determine the smallest molecular weight which will satisfy the analysis figures. The value so obtained, however, is an empirical one, and the actual molecular weight may be a multiple of it. Schulz has estimated the molecular weights of edestin, oxyhæmoglobin, and egg albumin, to be 7300, 14,800, and 4900 respectively.

The molecular weight of oxyhæmoglobin may also be calculated in an analogous manner from its *iron content*. As has already been stated, this substance is a compound of a simple protein (*globin*), containing sulphur, and a pigment (*hæmatin*) in which iron is present (p. 814). Although it has not yet been proved experimentally, it is probable that each oxyhæmoglobin molecule consists of one molecule of globin and one molecule of hæmatin. On this assumption the sulphur content of oxyhæmoglobin (0·43 to 0·67 per cent.) corresponds to a molecular weight of 14,800 to 9500, whilst the iron content (0·4 to 0·5 per cent.) corresponds to 14,000 to 11,200.

Molecular weights have also been calculated from the proportion of metal contained in the precipitates which are formed by adding salts of heavy metals (*e.g.* copper sulphate) to protein solutions.[1] This cannot be discussed in detail here.

Svedberg has developed an *ultracentrifuge method* of determining molecular weights. He concludes that a number of proteins are *monodisperse* (homogeneous with regard to molecular weight) when examined in the neighbourhood of the isoelectric point, and divides them into two groups : namely, those giving values of the order of millions, *e.g.* the hæmocyanins, and others the molecular weight of which is either 34,500 or this figure multiplied by 2, 3 or 6 (ovalbumin, 34,500 ; hæmoglobin, 68,000 ; serum albumin, 67,500 ; serum globulin, 103,800 ; edestin, 208,000). At higher and lower p_H values the protein molecule appears to break down, although in many cases this change is reversible. [2]

From these examples it will be seen that no exact estimation of the

[1] E. Harnack, " Untersuchungen über die Kupferverbindungen des Albumins," *Z. physiol. Ch.*, 1881, 5, 198. Schulz and Zsigmondy, *loc. cit.* [2] The Svedberg, *Trans. Farad. Soc.*, 1930, 26, 740.

magnitude of the protein molecule can yet be made. It remains for physical chemistry to discover a satisfactory solution of the problem.

Composition of Proteins.—The pure chemistry of the proteins is based on that of the amino-acids, which have already been dealt with on pp. 218 to 233. Some special characteristics of the proteins are discussed in the following pages.

Proteins in general contain the five elements, carbon, hydrogen, oxygen, nitrogen, and sulphur.[1] The percentage of each of these present varies for different types within the following limits :

Carbon	50·5 to 54·6 per cent.
Hydrogen	6·5 „ 7·3 „
Oxygen	21·5 „ 23·5 „
Nitrogen	15·0 „ 17·6 „
Sulphur	0·5 „ 2·2 „
Phosphorus	0·42 „ 0·85 „

The two other main groups of foodstuffs, fats and carbohydrates, differ from proteins in containing no nitrogen. In physiology, therefore, the quantity of nitrogen utilised by the organism gives a direct measure of the amount of protein metabolism.

The nitrogen in proteins occurs in various states of combination. Most of it is present in *peptide groups* derived from monamino acids and after hydrolysis of the protein the resulting free amino groups can be estimated by means of nitrous acid (van Slyke).[2]

The *basic nitrogen* is derived from the free amino groups contained in basic proteins, which are precipitated by phosphotungstic acid. The majority of these compounds are built up from molecules of diamino acids in such a way that only one of the two amino groups takes part in peptide union, the other remaining free. Nitrogen present in the latter state can be estimated by formol titration (Sörensen), or by means of nitrous acid (see above).

The *guanidine nitrogen* of basic proteins is contained in the free guanidine group of arginine.

Finally, it is possible that nitrogen may also be present in an *acid amide grouping*, such as is found in the half amides asparagine and glutamine (pp. 285, 286). The occurrence of the half amides of aspartic and glutamic acids in the protein molecule is strongly supported by the work of Osborne, Thierfelder[3] and others. Nitrogen in acid amide groups can be removed as ammonia by treating the protein with dilute mineral acids.

Some nitrogen may also occur in the form of *diketopiperazine groups*.

Owing to the formation of undefined by-products during hydrolysis these different nitrogen fractions cannot be estimated accurately.

The sulphur in proteins is derived from cystine, cysteine (thioserine),

[1] The nucleins, to be described later, contain phosphorus. Iron is present in hæmoglobin and copper in hæmocyanin. In addition, traces of iron are generally found in the ash of proteins.
[2] D. D. van Slyke, *Ber.*, 1910, 43, 3170; 1911, 44, 1684. [3] Thierfelder and v. Cramm, *Z. physiol. Ch.*, 1918, 105, 58.

and a third component which has been identified by Barger as γ-methyl-thiol-α-aminobutyric acid (*methionine*, see p. 241).

The instability of the protein molecule has rendered the investigation of the structure of these compounds a very difficult problem to attack by any method other than hydrolysis. Nevertheless, in recent years proteins have been acetylated and methylated, and the products reduced and subsequently hydrolysed, with a view to gaining information as to their constitution.[1] Proteins have also been halogenated.

Halogens [2] enter into the ring systems of cyclic amino-acids, and change the protein in such a way that sulphur can no longer be removed from it by treatment with alkalis. For a given method of halogenation the amount of halogen taken up by a particular kind of protein is constant.

Kossel and Edlbacher [3] have methylated proteins, chiefly protamines, by means of dimethyl sulphate. The N-methyl number, *i.e.*, the number of *N-methyl groups* corresponding to 100 atoms of nitrogen, was found to be a characteristic for each individual protein examined. It was shown that very similar compounds may give quite different N-methyl numbers.

Reactions of Proteins

No single one of the following reactions is in itself a reliable test for the presence or absence of proteins, but cases of doubt can be determined by the use of several of them.

The reactions of proteins are divided into precipitation and colour reactions. For determining the presence of proteins in animal fluids certain precipitation reactions only may be employed. Whereas the colour reactions depend on the occurrence of specific chemical groups in the protein molecule, and are therefore given also by the corresponding non-protein hydrolytic products, the precipitation reactions are due to the colloid nature of the protein and these alone give reliable information as to the presence of protein as such. Precipitation reactions are accordingly employed in medical science for the detection of protein matter in animal fluids (*e.g.* urine). Colour reactions should be applied exclusively to pure protein solutions.

Precipitation Reactions: 1. *Coagulation Test.*—Proteins are precipitated when heated in faintly acid solution, especially in the presence of neutral salts (see p. 791).

2. *Heller's Test.*—Proteins are coagulated by treatment with concentrated acid, *e.g.* nitric acid. This test is carried out as follows:—Concentrated nitric acid is gently poured down the side of the test-tube containing the protein solution. The acid forms a lower layer and a white disc of precipitated protein appears at the junction of the two liquids.

3. Proteins are precipitated by the addition of small quantities of

[1] Troensegaard, *Z. physiol. Ch.*, 1923, **127**, 84, 137. [2] See Cohnheim, *Chemie der Eiweisskörper* (Brunswick, 1911); see also Siegfried and Reppin, *Z. physiol. Ch.*, 1915, **95**, 18.
[3] *Z. physiol. Ch.*, 1918, **107**, 52.

salts of heavy metals, such as ferric chloride, ferric acetate, copper sulphate, copper acetate, mercuric chloride, and basic lead acetate.

4. Owing to their character as weak bases, proteins are precipitated by the *alkaloid reagents*, *e.g.* phosphotungstic acid and phosphomolybdic acid (in the presence of mineral acid), tannin, hydroferrocyanic acid, and picric acid. As phosphotungstic acid brings about complete precipitation, it is frequently employed for the removal of dissolved protein, more especially of basic protein. The reactions with tannin and hydroferrocyanic acid are also very sensitive. The latter is usually carried out by treating the protein solution with potassium ferrocyanide and acetic acid. Potassium mercuric iodide, like trichloroacetic acid, is often used to remove proteins from physiological solutions. Protein in urine is detected by reactions 1 and 2, and by precipitation with hydroferrocyanic acid; more recently a 20 per cent. solution of sulpho-salicylic acid has been introduced for this purpose. The precipitation reagents are used in histology as fixatives.

Colour Reactions: 1. *Biuret Reaction.*—This has been described on p. 232. It is chiefly used for distinguishing between proteins and their partially hydrolysed products, as peptones and albumoses give a redder tint than the proteins. The biuret reaction, however, is not a reliable test for a protein, since it is also given by certain other substances.[1]

2. *Millon's Test.*—On boiling protein, either in the dissolved state or in solid form, with an aqueous solution of nitrous acid in mercuric nitrate, the coagulated protein and the liquid are coloured pink to dark red. This reaction is given by all compounds having phenolic groups in the molecule, and in the case of protein is due to the presence of tyrosine residues.

3. *Xantho-protein Reaction.*—On treating a protein solution with strong nitric acid, a yellow coloration is produced, occasionally in the cold, but usually only after heating. On addition of excess of sodium hydroxide the liquid becomes reddish brown, whereas with excess of ammonia it turns an orange colour. This reaction depends on the presence of tyrosine and tryptophane groups, but is not peculiar to proteins.

4. The *Adamkiewicz-Hopkins Reaction.*—With a mixture of concentrated sulphuric acid and glyoxalic acid (or a solution of glyoxalic acid in glacial acetic acid) proteins give a reddish violet coloration, slowly in the cold but more rapidly on warming. This reaction is due to the presence of tryptophane groups and hence is not given by gelatin, in which this group is absent.

5. The *Ninhydrin Reaction*[2] of Abderhalden and Schmidt. When heated with triketo-hydrindene hydrate (ninhydrin), proteins and all α-amino-acids give a blue coloration.

6. The *Lead Sulphide Test.*—When a protein solution is heated with an alkaline solution of a lead salt, *e.g.* lead acetate, a black precipitate or

[1] H. Schiff, *Ber.*, 1896, **29**, 298; 1897, **30**, 2455. [2] *Cf.* Abderhalden and H. Schmidt, *Z. physiol. Ch.*, 1913, **85**, 143. Halle, Löwenstein, and Pribram, *Biochem. Zeitsch.*, 1913, **55**, 357.

a dark brown coloration is produced, owing to the formation of lead sulphide.

7. The *Iodine Test.*—For microscopic detection proteins are mixed with tincture of iodine or a solution of iodine in potassium iodide. The coagulum develops a yellow colour.

Classification of the Proteins and the Characteristics of the Individual Groups

As yet it is not possible to classify the proteins on a purely chemical basis, although they could perhaps be grouped in accordance with the relative proportions of mono- and diamino-acids formed from them on hydrolysis. A better method is to base the classification on physico-chemical differences. In this way the proteins can be divided into two main groups and a number of sub-groups.

(a) *Simple Proteins*

I. True proteins :

(*a*) Albumins (serum albumin, ovalbumin lactalbumin); (*b*) globulins (serum globulin, ovoglobulin, lactoglobulin, cytoglobulin); (*c*) plant globulins and plant vitellins ; (*d*) fibrinogen ; (*e*) myosin ; (*f*) phospho-proteins, which contain phosphorus (caseinogen, vitellins); (*g*) histones ; and (*h*) protamines.

II. Albuminoids [1] :

(*a*) Collagen ; (*b*) keratin (from hair, feathers, horn, etc.); (*c*) elastin ; (*d*) fibroin (from silk); (*e*) spongin, conchiolin ; (*f*) amyloid ; (*g*) albumoid and melanins.

(b) *Conjugated Proteins*

Compounds of proteins with other and usually highly complex substances.

(*a*) Nucleoproteins ; compounds of proteins with nucleic acids ; (*b*) chromoproteins (hæmoglobins); (*c*) glucoproteins : compounds containing carbohydrates (mucins).

Only a short account of the different groups can be given here.

I.—SIMPLE PROTEINS

1. *True Proteins*

The **albumins** form a well-defined and readily accessible group of proteins, and, as already stated, may be obtained in a crystalline condition.[2] They are soluble in pure water, in dilute salt solutions, and in acids and alkalis. Pure solutions of albumins are neutral. They are not precipitated

[1] These are frequently grouped under the heading of unclassified proteins or *scleroproteins.* They differ from the " true proteins " chiefly in their physical properties, *e.g.* insolubility, and in their failure to give certain of the typical protein reactions, but no sharp distinction can be drawn between the two groups. [2] For the distillation of ovalbumin under diminished pressure see A. Pictet and M. Cramer, *Helv. Chim. Acta*, 1919, **2**, 188.

from these solutions by saturation with salt or magnesium sulphate, nor by half saturation with ammonium sulphate. In this last respect they differ from the globulins, which are frequently associated with them in nature. On the other hand, the albumins are completely precipitated when their solutions are saturated with ammonium sulphate. On treatment with caustic soda, ovalbumin gives *egg-protalbinic acid* and *egg-lysalbinic acid*.[1] The albumins so far investigated contain a large percentage of sulphur and yield no glycine on hydrolysis.

The **globulins** differ in a number of ways from the albumins. For example, they do not dissolve in pure water, although they are soluble in dilute solutions of neutral salts and of alkali carbonates. They behave as acids and are precipitated by carbon dioxide from very weakly alkaline solutions ; an excess of carbon dioxide, however, is to be avoided. They are very easily denatured, and may be precipitated from their solutions by dilution with water or by acidification. Globulins are completely salted out with magnesium sulphate at 30°, but with sodium chloride the precipitation is incomplete. They are precipitated when their solutions are half saturated with ammonium sulphate, a property which is used in the separation of globulins from albumins. This is the most pronounced difference to be observed between the two classes.

The **plant globulins,** which function as reserve material in the seed, are also very readily isolated. The best known of these is **edestin,** which is soluble at 60° in a 3 per cent. solution of sodium chloride, from which it may be obtained in a crystalline state. On partial hydrolysis with caustic soda edestin yields three products : a protalbinic acid which is very sparingly soluble in water, an albumose (lysalbinic acid) which is soluble in water and can be precipitated with ammonium sulphate, and a peptone which cannot be salted out.[2]

From plant seeds, such as barley and wheat, Osborne and his collaborators have isolated *prolamines*, or *gliadins*, a class of protein of which no representatives have yet been discovered in the animal kingdom. Unlike other proteins they are soluble in 75 per cent. alcohol, and contain a large proportion of glutamic acid (up to 40 per cent.).

Myosin, present in muscle, possesses the properties of the globulins, and plays an important part in the phenomenon known as *rigor mortis*.

Fibrinogen and *caseinogen* are distinguished by their property of clotting under the influence of certain ferments. This process is not to be confused with coagulation. The clotted substances are insoluble in water and salt solutions, and can be coagulated by heating or by treatment with alcohol. **Fibrinogen** is a protein contained in the blood of all vertebrates. In the presence of calcium salts and under the influence of a ferment, thrombase, it is converted into **fibrin ;** the clotting of blood is due to this change.

The **phosphoproteins** contain phosphorus. At one time they were

[1] Skraup and Hummelberger, *Monats.*, 1909, **30**, 125. [2] Skraup and Wöber, *Monats.*, 1909, **30**, 289.

known as nucleo-albumins and were grouped with the nucleoproteins. Unlike the latter, however, they are not found in combination with nucleic acid. Phosphoproteins are distinctly acid in character, and colour litmus red. They are insoluble in water, but readily dissolve in the form of their alkali and ammonium salts. From these solutions the addition of acids precipitates the original compounds. The salts are not coagulated on being heated in solution. This group includes *caseinogen* and *vitellin*, which is present in egg yolk.

Caseinogen [1] is the characteristic protein of milk, in which lactalbumin and lactoglobulin are also present. As yet it has not been definitely ascertained whether the milk of different animals contains one and the same caseinogen. The compound is present in milk in the form of the soluble calcium caseinogenate. On addition of acid, caseinogen is precipitated owing to its insolubility in water. Hence it may be purified by solution in alkali and reprecipitation with acid. Under the influence of rennin, a ferment secreted by the mucous membrane of the stomach, caseinogen is converted into *casein*.[2] The latter differs from caseinogen in the insolubility of its calcium salt. Consequently, if calcium salts are already present in the solution in which this change occurs, as is the case in milk, insoluble calcium caseinate or curd separates out. The conversion of milk into junket by means of extract of rennet is therefore a dual process, involving the production of casein from caseinogen and the precipitation of insoluble calcium caseinate. The action of rennin is assisted by the presence of small amounts of acids, and is retarded by alkalis. In the preparation of cheese the curd is fermented by more prolonged treatment. The artificial milk preparation, *eucasein*, is the ammonium salt of caseinogen ; *nutrose* and *plasmon* are sodium salts.

The souring of milk in summer, *i.e.* acid clotting, is to be distinguished from the curding produced by rennin. The former is a direct result of the fermentation of the lactose by micro-organisms, leading to the formation of lactic acid which precipitates the caseinogen (see above). This process can therefore be delayed by the addition of sodium bicarbonate. The residual clear liquid is known as sour whey.

On the other hand, the residual liquid from cheese is known as sweet whey, owing to the absence of acid.

Numerous analyses have been made of caseinogen from cow's milk, the most reliable of which are probably the following due to Hammarsten :—C 52·96 per cent., H 7·05 per cent., N 15·65 per cent., S 0·758 per cent., P 0·847 per cent. In this connection, however, it must be remembered that caseinogen has not yet been obtained in the crystalline state. On hydrolysis with sulphuric or hydrochloric acid caseinogen yields a number of products, including *glutamic acid* and three different compounds of the composition of *leucyl valine anhydride*, $C_{11}H_{20}O_2N_2$.

[1] R. Scherer, *Das Casein. Dessen Zusammensetzung, Eigenschaften, Herstellung und Verwertung.* Second Edition, Vienna, 1919. [2] Part of this undergoes a further decomposition, E. Petry, *C.*, 1906, II, 803.

In addition to its use in the preparation of patent foods such as plasmon, sanatogen, etc., caseinogen is employed in large quantities in the manufacture of artificial bone and ivory goods, and electrical insulating material.

The last two groups of simple proteins, viz., the *histones* and *protamines*, contain a large proportion of diamino-acids and are basic in reaction. They appear to be of relatively simple structure.

Histones always occur in nature in combination with other compounds, as in the spermatozoa of fish. Globin, the protein component of the red colouring matter of blood, also belongs to this group. Histones have a pronounced basic character and are soluble in acids. From aqueous solutions they are precipitated by addition of ammonia, but redissolve in excess of the reagent. They are not coagulated by boiling, except in the presence of salts. It is not at present possible to give a clear definition of a histone, but these compounds appear to occupy an intermediate position between the protamines and other proteins (Kossel).

Protamines have hitherto been found only in combination with nucleic acids in the spermatozoa of fish. The individual protamines are named after the fish from whose testicles they are obtained, *e.g. salmine* from salmon, *sturine* from sturgeon, and *clupeine* from herring. They have been investigated more particularly by Kossel.[1] A quantitative examination of the products obtained by hydrolysing protamines by means of acids or trypsin has shown that they contain approximately $\frac{8}{9}$ of their nitrogen in the form of arginine, together with small quantities of monamino-acids. The formula of salmine is possibly $(C_{81}H_{155}N_{45}O_{18})_x$ or $(C_{98}H_{186}N_{54}O_{21})_x$, in which x may be 1 or greater than 1. The protamines are strong bases but very little is known as to their properties in the free state. The best known salts are the sulphates, which can be purified by precipitation with alcohol from sulphuric acid solution. The hydrochlorides are more readily soluble than the sulphates. Solutions of the salts are laevorotatory. The platinum double salts of the protamines are either insoluble or sparingly soluble in water, and have been frequently used for analysis. The compound of this type formed by salmine approximates in composition to $2(C_{81}H_{155}N_{45}O_{18})$, $23HCl$, $11PtCl_4$.

Protamines cannot be coagulated by heat, but may be salted out by use of ammonium sulphate or sodium chloride. For their methylation see p. 796.

2. *Albuminoids*

The albuminoids are only found in animal bodies, in which they are present in the undissolved state. They constitute the framework of animal tissue, and play the same part in the animal body as certain carbohydrates (*e.g.* cellulose) do in the vegetable kingdom. They cannot be dissolved without undergoing chemical change, and differ from other proteins chiefly in their resistance towards chemical reagents. As already mentioned, there are different kinds of albuminoids.

[1] Kossel has given a summary of his results in "Ueber die einfachen Eiweisskörper," *Biochem. Centralblatt*, 1906, V. For sturine see Kossel and Weiss, *Zeit. f. physiol. Ch.*, 1912, **78**, 402.

Collagen is the most widely distributed of these compounds. It forms the basis of bone and cartilage, and is the chief constituent of the connective tissues. When boiled with water collagen passes more or less readily into solution, hydrolytic decomposition probably taking place during this process. The soluble product is known as **gelatin** (*glutin*). On being cooled to room temperature the solution sets to a jelly, which again liquefies on warming. Gelatin is not thrown out of solution by nitric or other mineral acid, but is precipitated by mercuric chloride in the presence of hydrochloric acid, and also by tannin.

The collagens obtained from different organs and different animals are not necessarily identical. Collagen differs from the " true proteins " more especially in its high content of nitrogen (17·9 per cent.). On hydrolysis it yields, in addition to other products, an exceptionally high proportion of glycine (15 to 18 per cent.). On the other hand, collagen contains neither tryptophane nor tyrosine residues, and the protein reactions due to the presence of these amino-acids are therefore not given by it.

Keratin is contained in most of the horny structures produced by the epidermal cells of the skin, *i.e.* horns, hoofs, nails, feathers and hair. It is insoluble in water, dilute acids and alkalis, but when boiled with alkalis or heated under pressure with water it undergoes decomposition and passes into solution. Keratin contains a very high proportion of sulphur (4 to 5 per cent.), the greater part of which can be removed in the form of hydrogen sulphide by boiling with alkali, or even with water. According to Drechsel, another substance belonging to this group is **gorgonin,** the insoluble protein in coral. Similarly **iodospongin,** the skeletal tissue of the tropical horn sponge, is probably to be classified with the keratins. It was shown by Mörner that gorgonin, iodospongin, and other proteins of the skeletal tissue of anthozoa all contain halogens. From the hydrolysis products of these compounds have been isolated 3 : 5-*diiodo-tyrosine* (*iodo-gorgonic acid*), and 3 : 5-*dibromo-tyrosine* (*bromo-gorgonic acid*).

Elastin forms the elastic fibres of animal connective tissue, and is generally prepared from the cervical ligament of the ox. Like keratin, it is insoluble in dilute acids and alkalis, but contains a comparatively high carbon and low sulphur content. When elastin is warmed with dilute alkalis the sulphur is completely removed.

Fibrosin or **silk fibroin** is the chief constituent (about 53 per cent.) of silk, and has been more fully investigated than any other albuminoid. When silk is boiled for several hours with water, *silk gelatin* or **sericin** passes into solution, leaving behind the insoluble silk fibroin. The latter is insoluble in dilute but soluble in concentrated acids and alkalis. It is precipitated from its solutions on neutralisation, or addition of alcohol. By partial hydrolysis of fibrosin Abderhalden [1] obtained d-*alanyl-glycine*, and d-*alanyl-glycyl*-l-*tyrosine*. The latter, which has also been prepared synthetically, was the first tripeptide to be obtained by the partial hydrolysis of a protein.

[1] Abderhalden, *Z. physiol. Ch.*, 1911, **72**, 1.

Spongin is the chief constituent of the common sponge, and resembles keratin in many respects. At ordinary temperatures it only dissolves in very concentrated sulphuric or hydrochloric acid, but it is more readily soluble in alkali. *Conchiolin* is the organic component of the shells of the mussel and snail; *cornein* is the corresponding constituent of coral.

Amyloid takes its name from the fact that under certain conditions it yields a blue coloration with iodine (*cf.* starch, amylum). It does not occur normally in the body but is produced under pathological conditions. Whereas healthy tissue is coloured blue with methyl violet, tissue containing amyloid is coloured ruby red.

In the group of albuminoids are included a large number of other proteins, of which so little is known that they cannot be discussed here.

II.—CONJUGATED PROTEINS

As has already been stated, the conjugated proteins are compounds of proteins with other complex substances, the non-protein part of the molecule being known as the *prosthetic group*.

Nucleoproteins

Nucleoproteins are compound of proteins with nucleic acids, and are so named because they are the chief constituents of the cell nucleus in plant and animal organisms. They are all soluble in water and salt solutions, and dissolve with special ease in alkalis. They are strongly acid in character, may be salted out from their solutions, and are denatured by heat. Nucleoproteins are present in all cell nuclei and have been prepared from a number of very different organs, including the spermatozoa of fish. Among other compounds of this type, yeast nucleoprotein has been subjected to careful investigation, as the corresponding *yeast nucleic acid* is readily isolated from yeast.

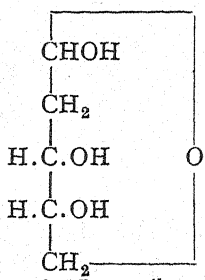
The manner in which the nucleoproteins are built up from the two components, protein and nucleic acid, is still uncertain. It appears, however, that the nucleic acid is combined with two parts of protein, one of which may be easily detached, leaving a compound still containing nucleic acid united with protein. The latter substance is known as a *nuclein*. On further hydrolysis the nuclein breaks down to give free nucleic acid.

The constitution of the **nucleic acids** [1] has been examined by Feulgen, Kossel, Levene, Osborne, Steudel, and others. According to the method of treatment these acids may undergo partial or complete hydrolysis.

Complete hydrolysis with dilute mineral acids results in the formation of *phosphoric acid*, *purine* and *pyrimidine bases*, and a *carbohydrate*. Among the purine derivatives have been found adenine, guanine, xanthine

[1] See also *Nucleic Acids*, by W. Jones (Longmans, Green). *Nitrogenous Constituents of the Living Cell*, Plimmer. *Nucleic Acids*, P. A. Levene and L. W. Bass (1931).

and hypoxanthine, and among the pyrimidine bases cytosine, uracil and thymine (see p. 774). The carbohydrates present have been identified by Levene as the pentose d-*ribose* and its reduction product d-2-*desoxyribose*. Although the latter component is very unstable and in the presence of mineral acids is readily converted into laevulinic acid, it was successfully isolated [1] from thymus nucleic acid by employing a very mild hydrolytic agent (intestinal juice). The occurrence of a pentose and a desoxypentose in the nucleoprotein structure indicates that a previously unsuspected significance must be attached to pentoses in relation to animal metabolism.

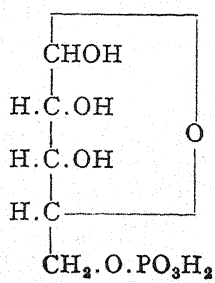


d-2-*Desoxyribose*

The nucleic acids are generally divided into two main groups, according to the nature of the carbohydrate present. Thus we have **ribose nucleic acids,** of which *yeast nucleic acid* is an example, and **desoxyribose nucleic acids**—such as the *thymonucleic acid* obtained from thymus gland or from fish sperm. The difference between these typical nucleic acids is illustrated by their hydrolysis products. Yeast nucleic acid yields a mixture of adenine, guanine, cytosine, uracil, *d*-ribose and phosphoric acid, whereas thymonucleic acid gives adenine, guanine, cytosine, thymine, *d*-2-desoxyribose and phosphoric acid.

Partial hydrolysis of nucleic acids can be effected by use of mild reagents, and in this manner the intermediate compounds known as *nucleotides* and *nucleosides* have been isolated.

Nucleotides are compounds built up of one molecular proportion of carbohydrate united to one of phosphoric acid and one of a purine or pyrimidine base. When yeast nucleic acid is treated with aqueous ammonia (2½ per cent.) for one hour at 115° it is converted into an equimolecular mixture of the four mononucleotides, *adenylic acid*, *guanylic acid*, *cytidylic acid* and *uridylic acid*.[2] Yeast nucleic acid is thus described as a polynucleotide built up of four mono-nucleotide molecules. The problem of determining the manner in which the component parts are linked together in the simpler units has also been solved by the use of hydrolytic methods. For example, when the mono-nucleotide *inosinic acid*, obtained from muscle, is heated with aqueous 1 per cent. hydrochloric acid, the purine residue is detached leaving a ribose-phosphoric acid,[3] which has been shown to be 5-phospho-ribofuranose (see formula) by its conversion into phospho-ribonic acid on oxidation with nitric acid. Under this treatment any of the isomeric pyranose ribose-phosphoric acids would have produced a phospho-ribo-trihydroxyglutaric acid.



[1] Levene and E. S. London, *J. Biol. Chem.*, 1929, 81, 711; Levene and T. Mori, *ibid.*, p. 803. [2] P. A. Levene, *J. Biol. Chem.*, 1919, 40, 415; 1920, 41, 19. [3] Levene and Jacobs, *Ber.*, 1911, 44, 746; Levene and E. T. Stiller, *J. Biol. Chem.*, 1934, 104, 299.

Yeast nucleic acid, on the other hand, has been found to give rise to a 3-phospho-ribose. Hence it is concluded that the phosphoric acid residue in nucleotides may be united to the carbohydrate molecule in either position 3 or 5.

Certain of the nucleotides, such as guanylic acid and inosinic acid, exist naturally in the free state; these and others also occur in combination in nucleoproteins.

Nucleosides.—When the nucleic acids are hydrolysed under somewhat more vigorous conditions, *e.g.* by heating under pressure at 180° in ammoniacal or neutral solution, the nucleotides first formed part with phosphoric acid and yield *nucleosides*,[1] which are crystalline compounds of carbohydrate and base. Examples of this type are the purine ribosides *adenosine*, *guanosine*, *inosine* and *xanthosine*,[2] in each of which the union is glycosidic, *i.e.*, at the aldehydic carbon atom of the sugar, the ribose residue being linked to position 7 of the purine molecule. In the pyrimidine riboside *cytidine* and its deamination product *uridine* the ribose group is attached to position 3 of the base.[3] It appears that carbohydrates form more stable compounds with the pyrimidine than with the purine bases, the former being resistant to hydrolysis by dilute mineral acids.

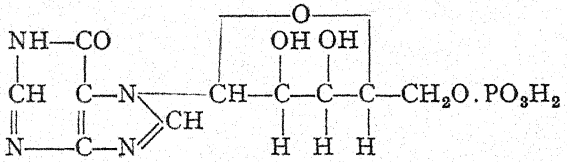
On evidence of this kind **nucleotides** are assigned the general structure:

phosphoric acid (a) *carbohydrate* (b) *base.*

Hydrolysis with ammonia disrupts the molecule at position *a*, eliminating phosphoric acid and leaving a nucleoside. Mild acid hydrolysis, on the other hand, attacks position *b*, except in the case of pyrimidine derivatives, and yields a ribose-phosphoric acid.

From the above description it will be seen that the nucleic acids vary in molecular complexity, since the group includes mononucleotides as well as polynucleotides. For this reason they are generally subdivided as follows:

1. **Simple Nucleic Acids or Nucleotides.**—Included in this group is *inosinic acid*, which was isolated by Liebig[4] from meat. Inosinic acid is a laevorotatory syrup of the structure: phosphoric acid—*d*-ribose—hypoxanthine.

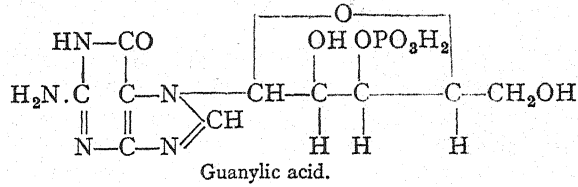


Inosinic acid.

It forms crystalline salts, the barium compound being sparingly soluble. *Guanylic acid*, of the composition: phosphoric acid—*d*-ribose—guanine,

[1] Levene and Jacobs, *Ber.*, 1909, **42**, 2469, 2703. [2] Adenosine and guanosine on deamination yield respectively inosine and xanthosine. [3] Levene and R. S. Tipson, *J. Biol. Chem.*, 1934, **104**, 385. [4] Liebig, *Ann.*, 1847, **62**, 317; Haiser and Wenzel, *Monats.*, 1908, **29**, 161.

was first prepared from the pancreas by Bang. It yields crystalline salts, and has itself been prepared in the crystalline condition from yeast nucleic



Guanylic acid.

acid by Levene. It is a constituent of various nucleic acids (*e.g.* thymonucleic acid, and nucleic acid from the pancreas), but also occurs in the free state in the pancreas and other organs. *Yeast-adenylic acid*, which can be obtained by partial hydrolysis of yeast nucleic acid, resembles guanylic acid in structure but contains an adenine residue instead of one derived from guanine.

2. The true **compound nucleic acids** or **polynucleotides** are divided, as already stated, into two groups according as the carbohydrate residue in the molecule is that of *d*-ribose (*e.g.* yeast nucleic acid) or *d*-2-desoxyribose (*e.g.* thymonucleic acid). Up to the present polynucleotides have only been obtained as amorphous dextrorotatory substances. They are sparingly soluble in water, practically insoluble in alcohol and ether, but soluble in ammonia and alkalis. They are precipitated from solutions of their salts by the addition of hydrochloric acid. The salts can be precipitated by means of certain dye-bases, and owing to the solubility of the product in alcohol this method is recommended by Feulgen for their purification. *Yeast nucleic acid*, which is apparently identical with the *tritico-nucleic acid* isolated from wheat embryo, is composed of four nucleotide molecules, containing *d*-ribose as carbohydrate and guanine, adenine, cytosine, and uracil as bases. Some other nucleic acids, including thymonucleic acid, appear to have a more complex structure built up of a large number of mononucleotide groups. The molecular arrangement of these compounds has not yet been established.

Hæmoglobins

These are compounds of proteins with pigments containing iron. *Hæmoglobin*, the red colouring matter of the blood of vertebrates, is the chief constituent of red blood corpuscles. It is built up from a protein, *globin*, and a prosthetic compound, *hæm*. Hæm contains iron, and will be described in detail on pp. 810 *et seq.* It is probable that the bloods of different animals contain different hæmoglobins. With oxygen, carbon monoxide and other gases, hæmoglobin combines to give loose addition compounds, such as oxyhæmoglobin and carboxyhæmoglobin. The most important of these is oxyhæmoglobin, which contains one molecule of hæmoglobin to one of oxygen. It readily gives up its oxygen again [1] and thus plays an essential part in the respiration of the vertebrates. This compound is often loosely termed hæmoglobin.

[1] Conant and Fieser, *J. Biol. Chem.*, 1925, **62**, 595.

When blood is allowed to stand in air the unstable oxyhæmoglobin, in which iron is in the ferrous state, readily changes into the stable methæmoglobin,[1] containing ferric iron. Hence the latter has been largely used in analyses and other investigations on the colouring matter of blood. Owing to the extremely high molecular weight of these compounds, there is very little difference between the percentage composition of hæmoglobin and methæmoglobin. Hæmoglobins from different kinds of animals differ considerably in their solubility in water. These differences are due to variations in the protein part of the molecule. Hæmoglobin is not salted out from a neutral solution by the addition of sodium chloride or magnesium sulphate, but only by saturation with a mixture of magnesium and sodium sulphates.

Under the influence of acids methæmoglobin decomposes into globin and hæmatin. With hydrochloric acid, for example, it yields globin and an ester-type of compound of hæmatin and hydrochloric acid, known as *hæmin*. The latter is described in the following chapter, but it may be noted that its property of separating in characteristic reddish-brown microcrystalline needles is of importance for the detection of blood stains in forensic medicine.

The compound formed by union of hæmoglobin with carbon monoxide is more stable than oxyhæmoglobin; and the poisonous character of carbon monoxide is due to the ease with which it displaces oxygen from oxyhæmoglobin, thus preventing oxygen from being carried to the tissues.

Glucoproteins

Glucoproteins are compounds of proteins with carbohydrates. As might be expected, their nitrogen content (11·7 to 12·3 per cent.) is less than that of the true proteins. The group consists essentially of the *mucins*, present in the mucous membranes, together with the related compounds, pseudo-mucins, mucoids and chondroproteins. It has already been stated on p. 306 that ordinary mucins yield *glucosamine* on hydrolysis; in a similar manner the mucin from frog spawn yields *galactosamine*. The *chondroproteins* contain chondrosamine, a sugar of a different configuration, which appears to be closely related to galactosamine.[2]

The *mucins* are widely distributed in nature and are known to be constituents of mucus and saliva. They are markedly acid in character, do not dissolve in pure water, but dissolve readily in alkali carbonates and ammonia. From these solutions they are precipitated by the addition of excess of acetic acid. They are not coagulable by heat. The mucins are very closely related to the chondroproteins. Of the latter, the most carefully investigated representative is *chondromucoid*, which with collagen is one of the chief constituents of cartilage. On hydrolysis it yields protein and *chondroitin sulphuric acid*,[3] an acid ester of sulphuric acid with

[1] Conant and Fieser, *J. Biol., Chem.*, 1925, **62**, 595. [2] Compare P. A. Levene, *J. Biol. Ch.*, 1917, **26**, 143. [3] For further details see Orgler and Neuberg, *Z. physiol. Ch.*, 1903, **37**, 399. Levene and La Forge, *J. Biol. Ch.*, 1913, **15**, 69, 155; 1914, **18**, 123; 1915, **20**, 433.

carbohydrate, containing also amino-acid residues. When chondroitin sulphuric acid is boiled for a short time with acids, it is hydrolysed further to sulphuric acid and a sulphur-free component *chondrosin*.

The *melanins*, of which very little is known, form another group of compounds standing in close relationship to the proteins. They are dark brown or black pigments occurring in hair and skin, and are widely distributed throughout the animal kingdom. Products resembling naturally occurring melanins are obtained by the acid hydrolysis of almost all proteins; these dark products are grouped together under the name of *humin substances*.

Constitution of the Proteins

Recent researches have given rise to considerable discussion regarding the possible occurrence of heterocyclic groups in protein molecules. It is well known that diketopiperazines are found among the hydrolysis products of proteins and that cyclic compounds such as pyrazines and pyrroles are formed by methods of reductive disruption. The difficulty is to determine whether these cyclic products exist as such in the protein or come into being as a result of the decomposition processes.

I. *Diketopiperazines*.—Abderhalden has recently isolated a number of diketopiperazines from proteins by mild chemical or fermentative disruption. These include *alanyl-glycine anhydride*, obtained by hydrolysing dog's hair with 1 per cent. hydrochloric acid for eight hours in an autoclave at 150° to 160°, and *alanyl-leucine anhydride* and *alanyl-phenylalanine anhydride*, prepared in a similar manner from hog's bristles.[1] The isolation of these compounds, according to Abderhalden, indicates the existence of diketopiperazine structures in the original proteins. On the other hand, E. Fischer, and also Brigl [2] and Abderhalden, have demonstrated the ease with which diketopiperazines are formed as secondary products from polypeptides.

Abderhalden has obtained some confirmation of his views in the colour reactions given by diketopiperazines with picric acid, 3 : 5-dinitrobenzoic acid and similar compounds. Such reactions are also given by most of the proteins and peptones, but not by polypeptides or amino-acids. These conclusions, however, are opposed by various critics, including M. Bergmann.[3]

Methods of oxidative and more especially of reductive disruption have been utilised by Abderhalden. Using sodium and amyl alcohol as reducing agents, he obtained piperazines from diketopiperazines, but not from polypeptides or amino-acids. On applying this procedure to silk fibroin, silk peptone and gelatin, Abderhalden also succeeded in isolating piperazine derivatives, thus affording further evidence in support of the existence of diketopiperazine units in the proteins.[4]

[1] E. Abderhalden and E. Komm, *Zeit. f. physiol. Chem.*, 1925, **145**, 309. [2] P. Brigl, *Ber.*, 1923, **56**, 1887. [3] E. Abderhalden and Komm, *loc. cit.*; M. Bergmann, *ibid.*, 1925, **144**, 277. [4] E. Abderhalden and E. Schwab, *Zeit. f. physiol. Chem.*, 1925, **148**, 254.

Against these views it was formerly argued that the diketopiperazines are not attacked by enzymes, and thus differ from the majority of proteins. This objection, however, is not longer valid. In 1932 Abderhalden and Schwab [1] prepared three amino-acid derivatives of diketopiperazines, namely *l*-leucyl (glycyl-*l*-tyrosine anhydride), *l*-leucyl (glycyl-*l*-leucine anhydride) and leucyl (glycyl-serine anhydride). In these compounds the presence of the amino-acid residue attached to the diketopiperazine ring greatly diminishes the stability of the latter towards enzymes, and they are readily hydrolysed by erepsin and trypsin-kinase to form the corresponding tripeptides.

II. *Pyrroles.*—It has long been known that pyrroles may be obtained from proteins by dry distillation or hydrolysis. By the latter method E. Fischer isolated pyrrolidine carboxylic acid (proline) and hydroxy-pyrrolidine carboxylic acid, and Hopkins obtained the indole derivative tryptophane. More recently, Troensegaard [2] has advanced the suggestion that proteins are built up mainly of heterocyclic units, especially of pyrrole rings, and has devised methods of testing this hypothesis. The proteins (principally gliadin, gelatin, casein, and the proteins of blood) were first stabilised by acetylation and then subjected to vigorous reduction with sodium and amyl alcohol. The products so obtained were of a decided heterocyclic character and consisted largely of pyrroles.

III. *Other ring systems*, such as those present in the oxazolines and oxazoles are also considered by some chemists to enter into the structure of proteins.[3]

Despite these interesting researches, the problem of protein structure still remains undetermined. Against the newer ideas must be placed certain biological facts which indicate a fundamental relationship between proteins and amino-acids. Each living organism disrupts proteins into polypeptides and amino-acids, and again builds up its own protein matter from a mixture of amino-acids. The probability, therefore, is that these final products into which the organism disrupts proteins and from which it again synthesises them, form the chemical units from which the protein molecules are themselves elaborated. There still remains the possibility that a small group of proteins, including silk fibroin and keratin, contain a large proportion of diketopiperazine units, thus explaining their resistance towards enzymes.

X

Natural Colouring Matters

The following chapter is devoted to the chemistry of certain natural colouring matters and is divided into three sections, the first dealing with porphyrin derivatives of blood and leaves, the second with the carotenoids and the third with anthocyanins of flowers and berries.

[1] E. Abderhalden and E. Schwab, *Z. physiol. Chem.*, 1932, **212**, 61. [2] N. Troensegaard, *Zeit. f. physiol. Chem.*, 1920, **112**, 86; 1923, **127**, 137; **142**, 304; 1929, **184**, 147. E. Klarmann, *Chemical Reviews*, 1927, **4**, 102. See also Troensegaard, "Uber die Konstitution der Eiweissverbindungen," *Zeit. angew. Chem.*, 1925, **38**, 623. [3] M. Bergmann and co-workers, *Zeit. f. physiol. Chem.*, 1925, **143**, 108. P. Karrer and co-workers, *Helv. Chim. Acta*, 1924, **7**, 763; 1925, **8**, 205.

PORPHYRIN DERIVATIVES

HÆMOGLOBIN

Hæmoglobin, the colouring matter present in the red corpuscles of blood is a molecular compound of the protein, *globin*, with a pigment **hæm.** It very readily absorbs one molecular proportion of oxygen to yield **oxyhæmoglobin,** in which form oxygen is carried in the blood stream to various parts of the organism, where it is utilised with regeneration of hæmoglobin. When blood is removed from the organism, the oxyhæmoglobin contained in it changes into **methæmoglobin** in which oxygen is more firmly held. On being heated with acetic acid methæmoglobin breaks down to globin and a brownish red pigment **hæmatin,** $C_{34}H_{32}N_4O_4FeOH$; if sodium chloride is also present, a hydroxyl group of hæmatin is replaced by chlorine and **hæmin,** $C_{34}H_{32}N_4O_4FeCl$, is formed. Hæmin is thus the chloride of hæmatin, both compounds containing iron in the ferric state. Hæm, on the other hand, is a derivative of ferrous iron (see formula on p. 814).

An important advance was made in 1926 when Hill and Holden [1] successfully separated the *natural* globin from hæmoglobin and showed that this undenatured protein combined with neutral hæmatin (p_H 5 to 10) to form methæmoglobin (see p. 807). Similarly with hæm (p_H 9·0) it yields hæmoglobin itself. On the other hand, *denatured* globin unites with hæm to give **hæmochromogen.**[2] The chief interest of hæmochromogen lies in the fact that it is easily identified spectroscopically, even at extremely high dilutions. In legal cases, stains suspected of being due to blood may be tested by reduction with alkaline sodium hyposulphite, which converts the dried blood into hæmochromogen, followed by spectroscopic examination.

Hæmin can be obtained in the crystalline state by adding blood to a hot saturated solution of salt in glacial acetic acid. It is a tetra-pyrrole iron complex in which the metal is linked to nitrogen and the oxygen is present in the form of two free carboxyl groups.

When iron is removed from hæmin or hæm, compounds known as **porphyrins** are obtained. According to the acid reagent employed for this purpose (conc. H_2SO_4, HCl, HBr in glacial acetic acid) the resulting porphyrins exhibit minor differences in composition. They are readily identified spectroscopically and can be again transformed into their complex iron salts, **hæmins,** which show a close spectroscopic resemblance to natural hæmin. Iron can usually be introduced without difficulty so that hæmins and porphyrins must have similar molecular structures.

Hence it will be seen that reliable information as to the nature of hæmoglobin may also be obtained by investigating the corresponding iron-free **hæmatoporphyrin,** obtained from hæmin by use of hydrobromic acid. Certain porphyrins occur in the living organism, among which

[1] Hill and Holden, *Biochem. J.*, 1926, **20**, 1326. [2] Anson and Mirsky, *J. Physiol.*, 1925, **60**, 50; see, however, *Ann. Rep. Chem. Soc.*, 1927, 265, 267.

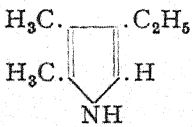
may be mentioned **coproporphyrin**, $C_{36}H_{38}N_4O_8$, present in fæces and urine, and **uroporphyrin**, $C_{40}H_{38}N_4O_{16}$, in urine.

Disruption Products of Hæmin.—Among earlier researches on the constitution of hæmin three degradation methods have proved of great value :

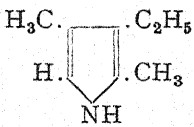
1. Reduction with hydriodic acid in glacial acetic acid, first employed by Nencki.
2. Küster's oxidative process, and
3. Disruption by alkylation as carried out by Hans Fischer and Röse.

The most successful disruptive method is the *reduction with hydriodic acid and acetic acid.* By treating hæmin in this manner Nencki obtained **hæmopyrrole,** which he regarded as a uniform product and isolated in the form of a mercury chloride compound and of a picrate. The occurrence of acid constituents in the reduction mixture was first established by Piloty, who isolated **hæmopyrrole carboxylic acid** by employing tin and hydrochloric acid as reducing agents. Nencki's method was subsequently re-examined by Willstätter, Hans Fischer and also by Piloty. As a result it was found that the hæmopyrrole of Nencki was not a homogeneous product but a complicated mixture. Other acid components were also discovered associated with hæmo-pyrrole-carboxylic acid. A summary of the reductive disruption products of hæmin isolated by these methods is given below.

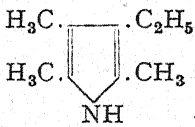
Reductive Disruption Products of Hæmin. Hæmopyrrole Bases



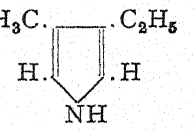
1. Hæmopyrrole



2. Kryptopyrrole

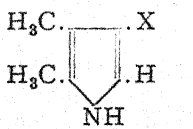


3. Phyllopyrrole

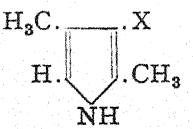


4. Opsopyrrole.

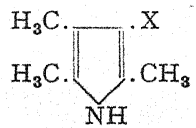
Hæmopyrrole Carboxylic Acids (X=$CH_2.CH_2.COOH$)



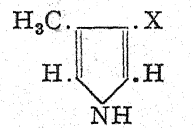
5. Hæmopyrrole carboxylic acid



6. Kryptopyrrole carboxylic acid



7. Phyllopyrrole carboxylic acid



8. Opsopyrrole carboxylic acid.

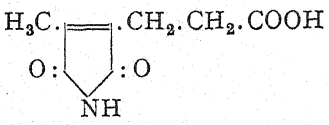
Good yields of alkylated decomposition products are obtained from hæmin by heating it under pressure at 230° with alcoholates, especially potassium methoxide. The latter reagent leads exclusively to the formation of phyllopyrrole and phyllopyrrole carboxylic acid, thus confirming the above results.[1]

Another valuable process is the *oxidation of hæmin and crude hæmopyrrole* first carried out by Küster.[2] The oxidative disruption of porphyrins in general has given much information concerning their structure.

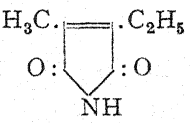
[1] H. Fischer and Röse, *Zeit. physiol. Chem.*, 1913, 87, 39. [2] W. Küster, *Ber.*, 1902, 35, 2948 ; 1907, 40, 2017.

Küster isolated **hæmatic acid** by oxidation of the colouring matters of blood and bile, and it has in addition been obtained from many porphyrins. The oxidative conversion of these compounds into hæmatic acid (9) and similar derivatives has not only proved of great value in determining their constitution, but also led to a more systematic examination of the products of reductive disruption (p. 811) and to the isolation of pyrrole-carboxylic acids from this source. Hæmatic acid has been synthesised by Küster [1] from acetoacetic ester.

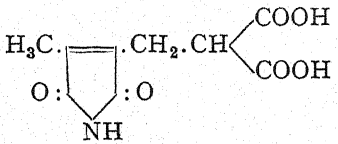
Oxidative Disruption Products



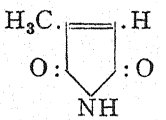
9. Hæmatic acid



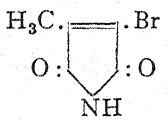
10. Methyl-ethyl-maleic imide



11. Carboxy-hæmatic acid



12. Citraconimide

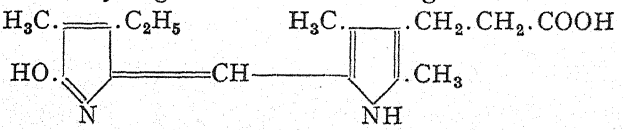


13. Bromocitraconimide.

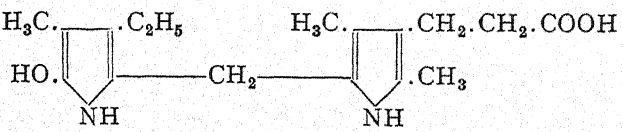
A further oxidation product is the carboxylated hæmatic acid formulated provisionally as in 11 above, which on being heated to a high temperature yields hæmatic acid and methyl-ethyl-maleinimide. It is obtained by oxidation of *uroporphyrin* and its synthetic analogue isouroporphyrin.[2]

Finally, citraconimide and bromocitraconimide (13) may be mentioned; these were obtained with hæmatic acid from deuteroporphyrin,[3] dibromodeuteroporphyrin and bromoporphyrin.[4]

Dipyrrole degradation products of hæmin and of porphyrins are not yet known, although **bilirubic acid** was discovered almost at the same time by Piloty [5] and H. Fischer [6] among the reduction products of the colouring matter of bile. The constitution of this compound together with that of its dehydrogenated derivative are given below.



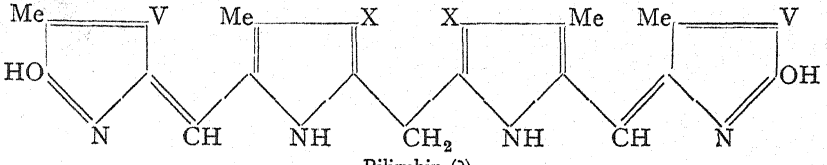
Xantho-bilirubic acid.



Bilirubic acid.

[1] Küster and Weller, *Ber.*, 1914, 47, 532. [2] H. Fischer and P. Heisel, *Ann.*, 1927, 457, 99. [3] H. Fischer and F. Lindner, *Zeit. physiol. Chem.*, 1926, 161, 18. [4] H. Fischer and F. Kotter, *Ber.*, 1927, 60, 1862. [5] Piloty and Thannhauser, *Ann.*, 1912, 390, 191. [6] H. Fischer and Röse, *Ber.*, 1912, 45, 1579; *Zeit. physiol. Chem.*, 1914, 89, 255.

The brown colouring matter of bile, **bilirubin,** $C_{33}H_{36}O_6N_4$, also resembles hæmin in yielding hæmatic acid on oxidation with chromic acid. It is probably a degradation product of hæmoglobin and is believed to have the structure

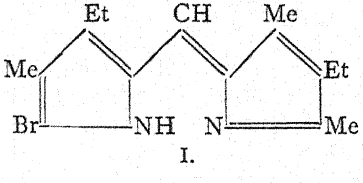


Bilirubin (?)
(V=CH : CH_2; X=CH_2.CH_2.COOH)

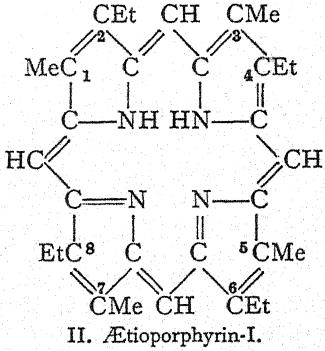
Comparison with the formula for hæmin given on p. 814 shows that the arrangement of the side chains attached to the pyrrole nuclei is the same in the two compounds.

A consideration of the disruption products described in the foregoing pages shows that hæmin and the porphyrins must possess very complex molecular structures. From the experimental evidence, however, Küster advanced a formula for hæmin which differed from that now accepted only in the relative positions of a vinyl and a methyl group attached to one of the four pyrrole nuclei.

Structure of the Blood Pigments.—In recent years the constitutions of hæm, hæmin and the porphyrins have been established by the brilliant synthetic work of H. Fischer, who has successfully developed methods for condensing substituted pyrroles to give various types of *dipyrryl methenes* and for converting these into porphyrins of known structure. For example, kryptopyrrole (p. 811) may be condensed by treatment with bromine to give a bromodipyrrylmethene (I), two molecules of which with formic or sulphuric acid undergo further condensation by loss of HBr between the 2-methyl and 2-bromo substituents to form **ætioporphyrin-I.**



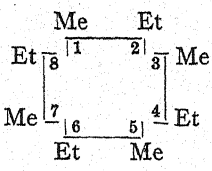
I.



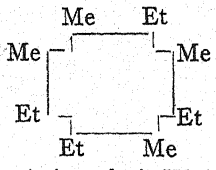
II. Ætioporphyrin-I.

Another method is by the fusion of 2 : 2′-dibromodipyrrylmethenes with 2 : 2′-dimethyldipyrrylmethenes in succinic acid. By these and similar reactions Fischer synthesised a number of ætioporphyrins, the structures of which he represented briefly as follows by a bracket formula showing the arrangement of the substituents in the pyrrole nuclei com-

posing the *porphin ring*. The unsubstituted compound, **porphin,** has also been synthesised. **Ætioporphyrin-I,** having an alternating system of methyl and ethyl groups, proved identical with the ætioporphyrin prepared from *coproporphyrin*. On the other hand, **ætioporphyrin-III** was identified with the ætioporphyrin from *hæmoglobin*. It contains two adjacent ethyl groups at 6 and 7, derived as will be seen from the formulæ given below from the two propionic acid groups present in hæmatin and protoporphyrin.

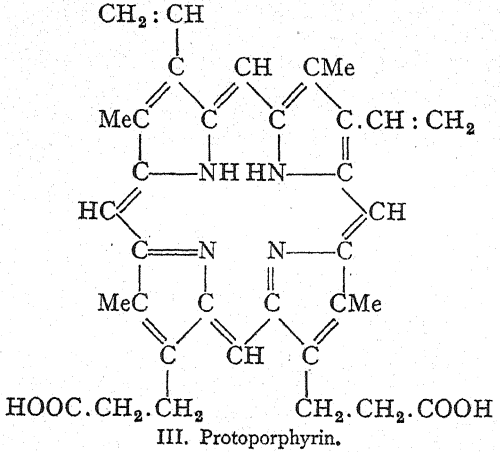


Aetioporphyrin-I

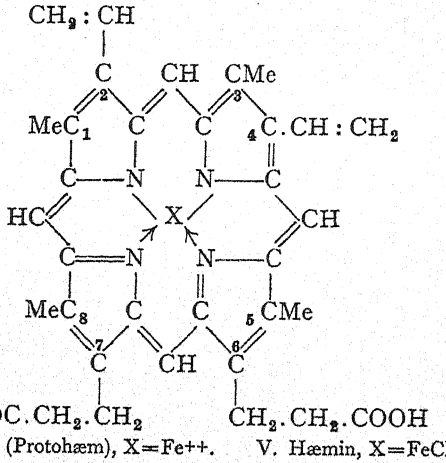


Aetioporphyrin-III.

Protoporphyrin (formula III) is an important porphyrin prepared from hæmin by treatment with dilute acid, which replaces the central



III. Protoporphyrin.

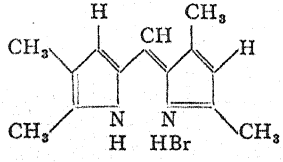


IV. Hæm (Protohæm), X=Fe++. V. Hæmin, X=FeCl++.
VI. Hæmatin, X=FeOH++.

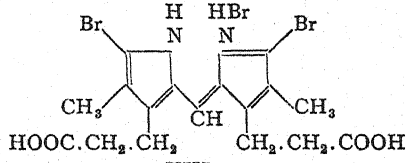
$FeCl^{++}$ group by 2H and leaves the vinyl groups intact. Under more vigorous conditions with hydrogen bromide in acetic acid hæmin yields

hæmatoporphyrin, resembling protoporphyrin in structure but with two $CHOH.CH_3$ groups in place of the vinyl groups. Protoporphyrin on reduction passes into **mesoporphyrin** (formula III with the two vinyl groups replaced by ethyl groups). Finally, the two propionic acid residues in mesoporphyrin may be converted into ethyl groups with loss of two molecules of carbon dioxide by heating the compound in a high-boiling solvent (*pyrolysis*). In this way **ætioporphyrin-III** or **mesoætioporphyrin** is produced.

The structures of all the above-mentioned compounds have been established by syntheses carried out by Fischer, with the aid of methods similar to those used for aetioporphyrin.[1] Under the influence of warm alcoholic hydrogen bromide 2 : 3-dimethylpyrrole readily condenses with 2 : 4-dimethylpyrrole-5-aldehyde to give the dipyrrolemethene hydrobromide VII. Another dipyrrolemethene hydrobromide, VIII, is obtained from kryptopyrrole carboxylic acid (see p. 811) by treatment with bromine, accompanied by the loss of a methylene group. When heated to 180-190° in succinic acid, VII and



VII.



VIII.

VIII condense to form a mixture of products from which deuteroporphyrin (formula III with both vinyl groups replaced by hydrogen) was isolated. This was next converted into the corresponding deuterohæmin [2] by treating it in acetic acid with ferrous acetate, with addition of a little sodium chloride and a drop of concentrated hydrochloric acid. The reason for this is that deuteroporphyrin is so much less reactive than the iron compound that it does not itself undergo the following step in the synthesis.[3] Acetylation in the two free positions, 2 and 4, was now effected by means of acetic anhydride and stannic chloride, and the resulting diacetyl-deuteroporphyrin was then reduced with alcoholic potassium hydroxide to hæmatoporphyrin ($CH_3CO \longrightarrow CH_3CHOH$). Finally, by heating at 105° in a high vacuum, the last compound lost water to yield protoporphyrin, which gave hæmin on introduction of iron into the molecule.

All the above formulæ contain a continuous alternation of single and double bonds, thus accounting for their strong colour. As in the case of benzene derivatives, the compounds are resonance hybrids and the exact bond arrangement cannot be stated with certainty.

CHLOROPHYLL

Chlorophyll, the chief pigment contained in green leaves, plays an important rôle in nature, absorbing energy from sunlight and utilising it for the synthesis of sugars and polysaccharides from the carbon dioxide of the air. Until very recently the molecular constitution of chlorophyll ranked as one of the unsolved problems of organic chemistry, but the rapid progress of the last few years has now made it possible to adopt a provisional formula for this compound. Much of our earlier knowledge

[1] For a summary see W. Treibs, *Z. angew. Chem.*, 1934, **47**, 294. [2] H. Fischer and Kirstahler, *Ann.*, 1928, **466**, 186. [3] Fischer and K. Zeile, *Ann.*, 1929, **468**, 99.

of the chemistry of chlorophyll is due to Willstätter,[1] who devised methods for isolating the pigment from leaves, proved that it consisted of two components *a* and *b*, and also made a very complete examination of its degradation products. The information thus gained was subsequently extended by the synthetic work of Hans Fischer on porphyrins derived from the colouring matters of blood and leaves, which finally led to the brilliant synthesis of hæmin and to a probable formula for chlorophyll.[2]

Willstätter has shown that the chloroplasts of plants consist of a colloidal mixture of colourless substances with four pigments, namely, two closely related chlorophyll colouring matters and two yellow compounds.

1. **Chlorophyll** a, $C_{55}H_{72}O_5N_4Mg$, a bluish-black solid forming greenish-blue solutions.

2. **Chlorophyll** b, $C_{55}H_{70}O_6N_4Mg$, a greenish-black solid forming pure green solutions.

3. **Carotene**, $C_{40}H_{56}$, an orange-red crystalline compound.

4. **Xanthophyll**, $C_{40}H_{56}O_2$, a yellow crystalline compound. These four pigments were found in every plant examined, irrespective of its botanical classification, although in certain algæ the proportion of chlorophyll *b* is exceedingly small. Fresh leaves contain about 2 parts per 1000 of chlorophyll *a*, $\frac{3}{4}$ of a part of chlorophyll *b*, $\frac{1}{3}$ of xanthophyll and $\frac{1}{6}$ of carotene.

Chlorophyll contains about 2·7 per cent. of magnesium and gives an ash of pure magnesia, no phosphorus or iron being present. On hydrolysis it yields the alcohol *phytol*, $C_{20}H_{40}O$ (see p. 155), in quantities corresponding to about a third part of its molecule, and methyl alcohol. The other hydrolysis product is a nitrogenous carboxylic complex based on four pyrrole nuclei. The constitution of this fragment has been determined by an investigation of the decomposition products chlorin *e*, obtained from chlorophyll *a*, and rhodin *g* from chlorophyll *b*. The former is olive-green in solution and the latter red.

A common property of chlorophyll, hæmin and all their degradation products still possessing the porphin ring structure of four pyrrole nuclei, is that they exhibit characteristic sharply banded spectra by means of which they may be identified.

Isolation of Chlorophyll and Separation into its Components

On a large scale the starting material in the preparation of chlorophyll is usually the dry powdered leaves of the stinging nettle. A layer of finely ground leaves, about 2 kilograms, is placed on a stoneware filter and treated with aqueous acetone (80 per cent.) or alcohol (85 per cent.). The pigments are extracted almost quantitatively, giving a yield of about 13 gms. This method may also be applied to fresh leaves.

[1] Compare Willstätter and Stoll, *Untersuchungen über Chlorophyll* (Springer, Berlin, 1913).
[2] For recent surveys of the chemistry of chlorophyll see C. C. Steele, *Chem. Rev.*, 1937, **20**, 1; H. Fischer, *ibid.*, p. 41.

The purification of the crude chlorophyll, which was accomplished in 1911 by Willstätter,[1] is based on the colorimetric estimation of its solutions and their systematic concentration by taking advantage of the unequal distribution of their constituents between two immiscible solvents, such as petroleum ether and aqueous alcohol. By this means it is possible to remove admixed yellow and colourless compounds and to raise the chlorophyll content to 70 per cent. Final purification is effected by solution in ether and precipitation with petroleum ether.

While applying this method Willstätter observed that chlorophyll itself became divided into two components which distributed themselves unequally between methyl alcohol (90 per cent.) and petroleum ether. Systematic fractionation in this way led to the isolation of the components *a* and *b*. **Chlorophyll** *a* is bluish-green and **chlorophyll** *b* yellowish-green in colour, but despite this difference they are very similar in composition and probably represent different states of oxidation.

A more effective means of separating chlorophyll *a* and *b* has recently been discovered in the *chromatographic method*, which utilises the differently coloured adsorption layers formed when a solution of the mixed products is allowed to flow through a tube packed with powdered sugar. In this way chlorophyll *b* was for the first time obtained in a pure state.[2]

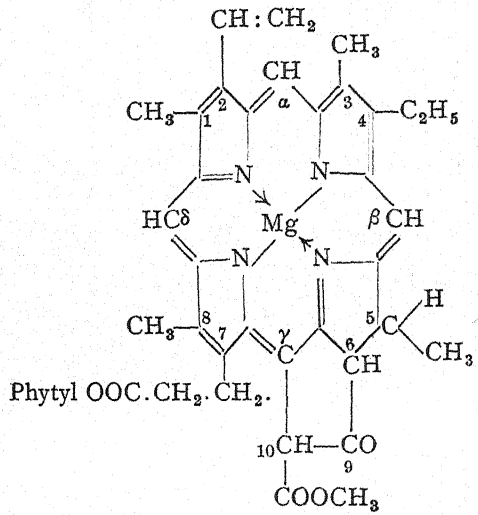
Molecular Structure of Chlorophyll

Our knowledge of the chemistry of chlorophyll owes much to the parallel investigations carried out on the colouring matter of blood, and reference should therefore be made to the account already given of the degradation products of hæmin (pp. 810 *et seq.*).

A definite relationship between the molecular structures of chlorophyll and hæmin was first indicated by the researches of Hoppe-Seyler in 1879 and of Schunck and Marchlewski fifteen years later, which led to the isolation from both sources of coloured disruption products known as porphyrins. This conclusion was supported by the work of Nencki and of Willstätter[3] on the reduction of hæmin and chlorophyll to mixtures of pyrroles (see hæmopyrrole, p. 811); and by Willstätter's oxidation of the phylloporphyrin[4] prepared from chlorophyll, which was found to yield methyl ethyl maleinimide and hæmatic acid, the same products as had previously been obtained by Küster from the colouring matter of blood. In addition, Willstätter succeeded in degrading chlorophyll to an ætioporphyrin which was believed to be the same as that derived from hæmin, although it was later established by Fischer that the compounds in question were closely related and not identical.

[1] Willstätter and Hug, *Ann.*, 1911, **380**, 177. [2] Winterstein and Stein, *Z. physiol. Chem.*, 1933, **220**, 263. Winterstein and Schön, *ibid.*, 1934, **230**, 139. See also Ruggli and Jensen, *Helv. Chim. Acta*, 1935, 624; 1936, 64. This separation was first demonstrated on a micro scale by Tswett in 1906, although the two components were not isolated from the adsorption tube. [3] Willstätter and Asahina, *Ann.*, 1911, **385**, 188. [4] Willstätter and Asahina, *Ann.*, 1910, **373**, 227.

Mention has already been made of the extensive investigations of Fischer on porphyrins and their derivatives, which led to the synthesis of many members of this group, including the ætioporphyrins of chlorophyll and hæmin. From the information thus obtained, supplemented by the researches of Conant, Stoll and others, a provisional formula for **chlorophyll** *a* has been advanced.



Provisional formula for Chlorophyll *a* (*Fischer*).[1]

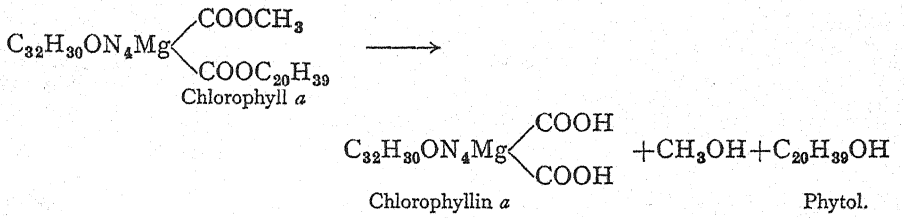
The relationship between chlorophyll and hæmoglobin may be summarised in the following terms. Chlorophyll is a wax, whereas hæmoglobin is a molecular compound of globin with the carboxylic acid hæm. Chlorophyll, as an ester, contains not only phytol but also methyl alcohol. Its nucleus is a dihydroporphin ring (the two extra hydrogens being placed at 5 and 6) and the side chains include one vinyl group instead of the two present in hæmin. The propionic acid group in position 6 of hæmin has become a β-ketopropionic acid group, which has united with the γ-carbon atom and undergone oxidation to form the isocyclic ring characteristic of chlorophyll. Finally, magnesium has replaced the co-ordinately bound iron.

Chlorophyll *b* is represented by Fischer as having the above formula in which the methyl group at 3 is replaced by a formyl group (.CHO). It is much more difficult to obtain in the pure state and has been less investigated.

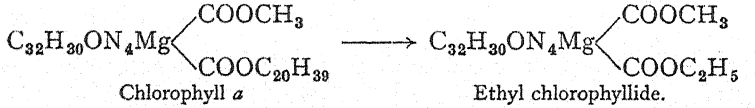
Decomposition of Chlorophyll by Alkalis and Acids.[2]—Chlorophyll, as has already been stated, is a diester containing methyl and phytyl groups. On hydrolysis with alkalis the alcoholic residues are removed, with the formation of salts of the carboxylic acids known as **chlorophyllins**

[1] H. Fischer, *Chem. Rev.*, 1937, **20**, 64. [2] For a schematic representation of the changes described in the following pages see Table on p. 823.

(*a* and *b*). These salts still contain magnesium and are chlorophyll-green in colour.



A change in the chlorophyll structure affecting the phytyl group has been found to take place if, during the extraction of the pigment from leaves, the materials are allowed to remain in contact for a considerable time. A secondary reaction then occurs owing to the presence in the leaves of an enzyme, *chlorophyllase*, which brings about partial alcoholysis of the chlorophyll, replacing the phytyl group by an alkyl radical corresponding to the alcohol used for the extraction. The resulting diesters are known as chlorophyllides, that obtained with ethyl alcohol being



ethyl chlorophyllide.[1] Unlike chlorophyll, which is amorphous in nature, the chlorophyllides deposit in the form of microcrystalline plates.

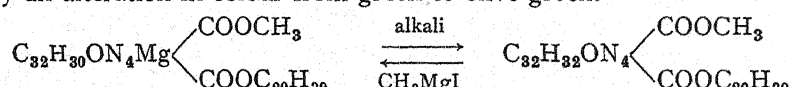
The above compounds still retain the vinyl group at position 2, the two extra hydrogen atoms at 5 and 6, and the complete isocyclic system (6, 9, 10, *γ*) of the chlorophyll molecule. The magnesium atom is comparatively stable to vigorous treatment with alkalis, although very easily removed by acids. On brief treatment with boiling alcoholic potassium hydroxide the product first formed from chlorophyll *a*, known as *isochlorophyllin a*, contains *three* carboxyl groups, due to rupture of the isocyclic ring (compare chlorin *e*, p. 820). Concentrated alcoholic alkali at higher temperatures, up to 240°, brings about a rearrangement of the hydrogen atoms, 2H being detached from positions 5 and 6, and added to the vinyl group at 2, converting it into an ethyl group. At the same time the carboxyl groups are progressively reduced by loss of CO_2 to two and finally to one. All these acids still contain one atom of magnesium for every four atoms of nitrogen, and are grouped together under the name of **phyllins,** some of them being named from their colour, *e.g.* **rhodophyllin,** (red). The corresponding oxygen-free derivative, **ætiophyllin,** $C_{30}H_{34}N_4Mg$, can be obtained from rhodophyllin after eliminating the last carboxyl group by heating in small quantities with soda-lime. In this final product it is obvious that the oxygen atoms have no part in the formation of the metallic complex. The magnesium in chlorophyll and its derivatives is therefore supposed to be united to nitrogen by covalent

[1] This is the *crystalline chlorophyll* discovered in 1881 by Borodin. The structure and origin of the compound were explained by Willstätter and Benz, *Ann.*, 1907, **358**, 267.

and co-ordinate valency bonds as indicated in the formula on p. 818. The above chemical changes, however, are more readily followed by use of the magnesium-free compounds.

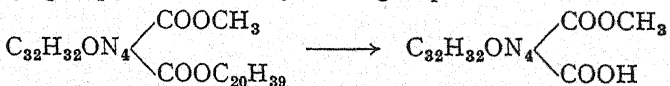
Under the influence of acids all phyllins lose magnesium to yield compounds known as **porphyrins.** Except in the case of the **ætioporphyrins** corresponding to ætiophyllin, these are acidic as well as basic in properties. Mixtures of porphyrins are purified by a method devised by Willstätter, according to which a fractional separation is effected by extracting the compounds in ethereal solution with hydrochloric acid of varying concentrations. This process takes advantage of the different basicities of the individual constituents.

Chlorophyll itself behaves in a similar manner when treated with dilute mineral acids, the ester groups remain unaffected but magnesium is removed leaving **phæophytins** (*a* and *b*), the change being accompanied by an alteration in colour from green to olive-green.



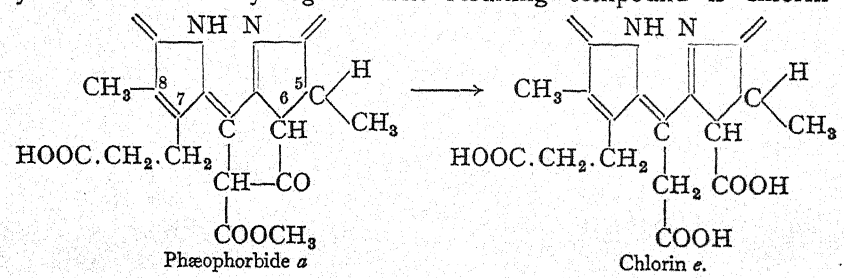
Chlorophyll *a* Phaeophytin *a*.

It is an interesting fact that chlorophyll can easily be regenerated from phaeophytin by bringing the latter into reaction with methyl magnesium iodide. Vigorous treatment with concentrated acids detaches the more easily hydrolysed phytyl group, forming **phæophorbide,** containing one free carboxyl group and one methyl ester group.



Phæophytin *a* Phæophorbide *a*.

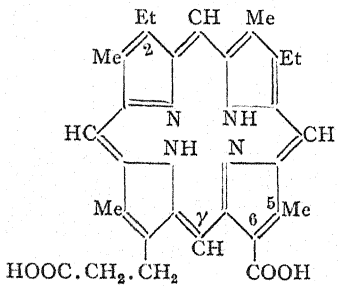
A more fundamental modification of the structure takes place when phaeophorbide *a* is heated for 30 seconds with methyl alcoholic potassium hydroxide. Two changes then occur, the methyl ester group is hydrolysed and the isocyclic ring is disrupted with the formation of a third carboxyl group. Fischer represents the rearrangement undergone by this portion of the molecule as follows, the rest of the structure being as shown for chlorophyll *a* (p. 818), except for the replacement of covalent magnesium by two atoms of hydrogen. The resulting compound is **chlorin** *e*,



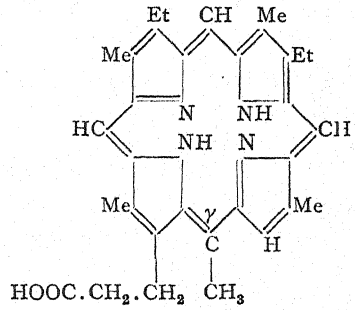
Phæophorbide *a* Chlorin *e*.

(*phytochlorin* e), a tricarboxylic acid. In the same way chlorophyll *b* may be degraded to the tricarboxylic acid **rhodin** *g*.

Still more drastic treatment of chlorophyll or the above intermediate products by heating in a sealed tube with alcoholic alkali leads to the successive elimination of CO_2 from the carboxyl groups, accompanied by loss of the two hydrogen atoms at 5 and 6 and the saturation of the vinyl group at 2. In this way are obtained **rhodoporphyrin,** $C_{30}H_{32}N_4(COOH)_2$, **pyrroporphyrin,** $C_{30}H_{33}N_4(COOH)$, and **phyllo-**



I. Rhodoporphyrin

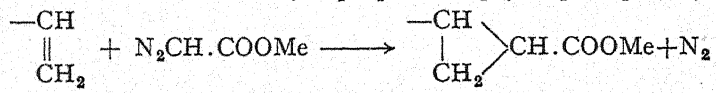


II. Phylloporphyrin.

porphyrin, $C_{31}H_{35}N_4(COOH)$. The structures of the first and third are shown above; pyrroporphyrin is a lower homologue of phylloporphyrin, having H in place of the CH_3-group attached to the γ-carbon atom.

The last carboxyl group can be eliminated, either by pyrolysis in high boiling solvents or by distillation with soda lime, yielding **pyrroætioporphyrin** and **phylloætioporphyrin** (formulæ as in I and II above, but with carboxyl groups replaced by hydrogen). The latter compound is thus a higher homologue of the former. It can be converted into pyrroætioporphyrin by heating with sodium ethoxide, when the γ-methyl group is displaced by hydrogen. This reaction also explains the production of two series of degradation products from chlorin *e*, one of which contains the γ-methyl group and the other does not.

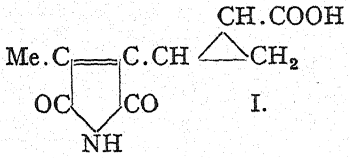
Reference to the above formulæ shows clearly how methylethyl maleic imide and hæmatic acid arise from the oxidation of porphyrins with chromic acid. The presence of a free methine hydrogen atom at position 6 in pyrro- and phyllo-porphyrins was established by brominating the compounds, followed by oxidation and the isolation of bromocitraconimide (see p. 812). The actual arrangement of the methyl, ethyl and propionic acid substituents around the porphin ring was determined by the brilliant syntheses of porphyrins carried out by H. Fischer. The existence of a vinyl group in methyl phæophorbide and the ester of chlorin *e* has been proved by treatment with methyl diazoacetate, when the vinyl double bond reacts to form a cyclopropane ring (compare p. 650).



which can be isolated in the form of methylmaleicimide-cyclopropyl carboxylic acid (I) on vigorous oxidation of the addition product.[1]

[1] H. Fischer and Medick, *Ann.*, 1935, 517, 245.

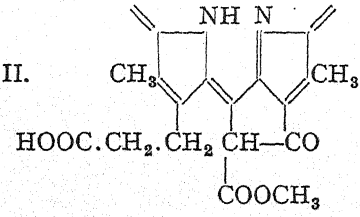
The above degradations of chlorophyll and phæophorbide to porphyrins did not serve to establish the presence of a porphin ring in chlorophyll itself, because the drastic treatment with alkali might conceivably have led to a breakdown of the molecule followed by a secondary synthesis of a porphyrin. A direct connection between the two series has been deduced by other methods.



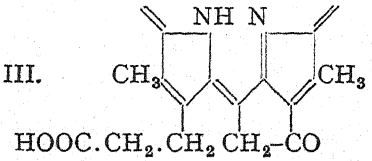
I.

Thus by use of milder conditions Conant[1] found that when heated with diphenyl at 180° to 250° (*pyrolysis*) phæophorbide and chlorin *e* lost 1 and 2 molecular proportions of CO_2 respectively, and that the latter compound also gave rise to two isomeric products, one of which was a porphyrin. Fischer and Conant independently reduced chlorophyll derivatives using hydriodic acid and glacial acetic acid at 60° (Fischer) or catalytic hydrogenation in presence of platinum (Fischer and Conant). In this way a leuco-compound was obtained from phæophorbide *a* which on aerial oxidation gave a series of phæoporphyrins, *e.g.* **phæoporphyrin** a_5,[2] $C_{34}H_{34}O_5N_4$; similarly, chlorin *e* yielded chloroporphyrins.

Phæoporphyrin a_5 which has been assigned formula II (with the upper part of the molecule as for rhodo- or phyllo-porphyrin) can be readily decarboxylated to give the stable compound **phylloerythrin**, III.



II.



III.

Phylloerythrin is a ketone; it yields an oxime and can be reduced to *deoxyphylloerythrin* ($CH_2.CO \rightarrow CH_2.CH_2$). When treated with sodium ethoxide in the presence of air phylloerythrin is converted into phyllo-, pyrro- and rhodoporphyrins by disruption of the isocyclic ring, a change which establishes the position of the ketonic oxygen as being attached to C9.

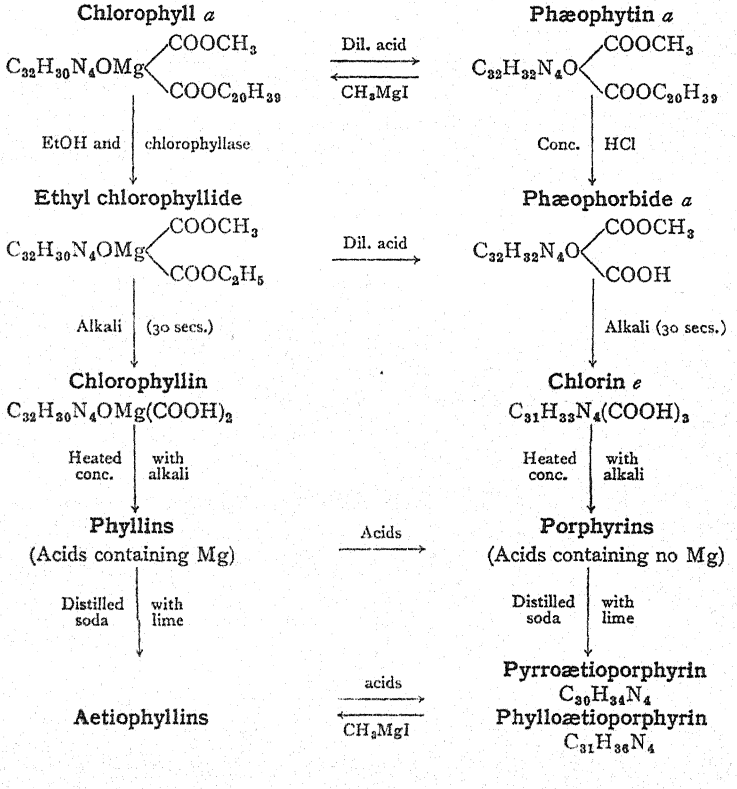
The formation and properties of phylloerythrin, the structure of which has also been confirmed by synthesis, constitute an important argument in support of the porphin-ring character of the chlorophyll molecule, and throw further light on the structure of the attached isocyclic ring. The close biological relationship between chlorophyll and phylloerythrin is emphasised by the fact that the latter was first discovered by Marchlewski in ox-bile, and that it occurs in the fæces of ruminants, especially in sheep dung. It is proved to be a porphyrin by its chemical properties and absorption spectrum, and it can also be obtained directly from

[1] J. B. Conant and J. F. Hyde, *J. A. C. S.*, 1929, 51, 3668. [2] The figure 5 indicates the number of oxygen atoms. The formula given represents the free acid, actually isolated as the monomethyl ester.

chlorophyllide and the phæophorbides (both of the chlorophyll type) by prolonged boiling with 20 per cent. hydrochloric acid.

The main outlines of the structure of chlorophyll as expressed in the formula on p. 818 are accepted by all workers in this field, but there is still some discussion as to the position of the two extra hydrogen atoms in the dihydroporphin ring, which are represented by Fischer as being linked to C_5 and C_6.

DEGRADATION PRODUCTS OF CHLOROPHYLL *a*



CAROTENOIDS [1]

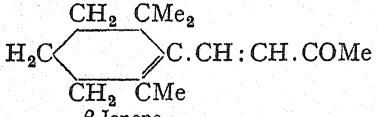
The carotenoids or yellow constituents accompanying the green colouring matter of leaves are found associated with chlorophyll in the chloroplasts. They are widely distributed in plants and a number of them are obtained as by-products in the preparation of chlorophyll. Structurally, the carotenoids belong to the class of compounds known as *polyenes*, and their characteristic colour is due to the presence in the molecules of a series of conjugated double bonds.

[1] Willstätter and Stoll, *Untersuchungen über Chlorophyll* (Berlin, 1913); L. S. Palmer, *Carotinoids and Related Pigments* (New York, 1922). For recent surveys see E. H. Farmer, *Ann. Rep. Chem. Soc.*, 1933, 145. A. Winterstein, *Z. angew. Chem.*, 1934, 47, 315. F. S. Spring, *Ann. Rep. Chem. Soc.*, 1935, 291. Leaf Xanthophylls, Carnegie Institute of Washington Publication No. 490, 1938 (H. H. Strain).

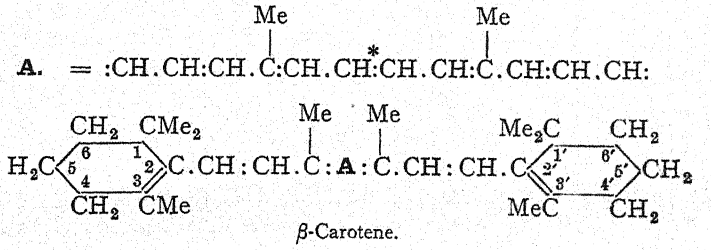
All green leaves and various other parts of plants contain these nitrogen-free crystalline pigments, which possess many properties in common but may be separated by taking advantage of their different solubilities or by chromatographic adsorption on lime or aluminium oxide. Among the chief members of this group are the *hydrocarbons*, α-, β- and γ-**carotenes** and **lycopene**; the *alcohol*, **xanthophyll**; and the *carboxy derivatives* **crocetin** and **bixin**.

Carotene, $C_{40}H_{56}$, is a yellow highly unsaturated hydrocarbon which is present in the carrot, butter and green leaves, as well as in a number of flowers and fruits. It was isolated from carrots as early as 1831. It exists in at least three closely related forms, a dextrorotatory α-carotene and the optically inactive α- and γ-carotenes, which can be readily separated by chromatographic adsorption on calcium hydroxide from a petroleum solution.[1] Recent researches have shown that carotenes are intimately related to vitamin-A, into which they are transformed by hydrolysis in the organism.

After the empirical formula had been determined by Willstätter, the catalytic hydrogenation of carotene (as well as of lycopene and xanthophyll) was examined by Zechmeister in 1927. β-Carotene and xanthophyll were found to contain eleven ethylenic double bonds and were concluded to have two cyclic groups in their molecules. The cyclic structures were later shown to be β-ionone rings, this possibility having been suspected from the smell of violets which is developed when carotene undergoes auto-oxidation.


β-Ionone

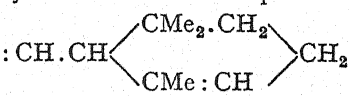
β-Carotene.—The complete structure of β-carotene, m.p. 187°, was deduced by Karrer[2] from the behaviour of the compound on oxidation. With cold aqueous potassium permanganate, β-ionone was formed, and at a higher temperature a mixture of acetic acid (4 mols.), 1 : 1-dimethylglutaric acid, dimethyl succinic acid and a little dimethyl malonic acid was obtained. These dibasic acids are also formed by the oxidation of β-ionone, and acetic acid is known to result (in many cases quantitatively) from methyl groups attached to a polyene chain. Ozonisation led to the production of *geronic acid*, $CH_3.CO.CH_2.CH_2.CH_2.CMe_2.COOH$, owing to rupture of the β-ionone ring. It has been found that the con-


β-Carotene.

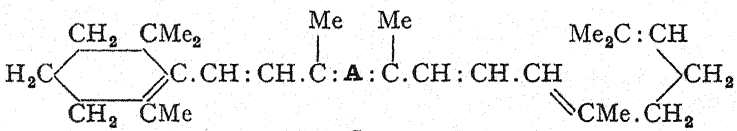
[1] See I. M. Heilbron, *J. S. C. I.*, 1937, 160 T. [2] P. Karrer and co-workers, *Helv.*, 1930, **13**, 1084; 1931, **14**, 1033. R. Kuhn and H. Brockmann, *Ann.*, 1935, **516**, 95.

jugated central portions of the molecules of polyene pigments are generally built up of isoprene units arranged symmetrically about the middle (*) of the chain. In order to save space they are conveniently formulated as shown in the preceding structure for β-carotene, in which the central portion is given separately as A.

α-Carotene melts at 183° and is optically active. Karrer represents it as having the same formula as the β-isomeride except that one of the two β-ionone rings is replaced by an α-ionone ring. The asymmetric carbon atom of this ring which is attached to the polyene chain accounts for the optical activity. On ozonisation the α-ionone ring gives rise to *isogeronic acid*,[1] $CH_3.CO.CH_2.CMe_2.CH_2.CH_2.COOH$.

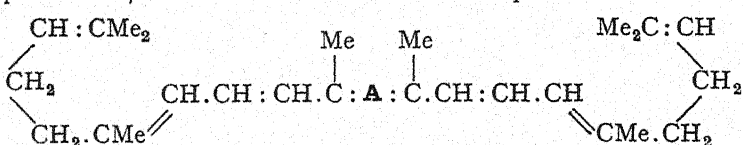

α-ionone ring

γ-Carotene, m.p. 178°, resembles the β-compound in being optically inactive. One half of its structure is that of β-carotene, the other half is an open-chain arrangement [2] which is also present in lycopene (see below). γ-Carotene is present in very small quantities in the carotene mixture, but is readily separated by adsorption on aluminium hydroxide.


γ-Carotene

Only those polyenes, such as the carotenes, which possess at least one unmodified β-ionone ring in the molecule, appear to be capable of undergoing conversion into vitamin-A in the organism and hence of promoting growth. The closely related xanthophylls in which the rings are hydroxylated, are not physiologically active, nor is the open chain hydrocarbon lycopene.

Lycopene, $C_{40}H_{56}$, is isomeric with carotene and was first isolated from the tomato in 1876. It is a dark red compound which also occurs in rose hips, the berries of the bitter sweet and other plants. The molecule is assigned the following aliphatic structure in which both of the ionone rings present in β-carotene are severed to form open chains.


Lycopene.

Under the heading of *phytoxanthins* are included a number of related hydroxy derivatives of the polyene type, many of which occur in nature as esters of fatty acids.

[1] P. Karrer and co-workers, *Helv.*, 1931, **14**, 614, 833; 1933, **16**, 975. [2] A. Winterstein and U. Ehrenberg, *Z. physiol. Chem.*, 1932, **207**, 25; R. Kuhn and H. Brockmann, *Ber.*, 1933, **66**, 407.

Kryptoxanthin, $C_{40}H_{55}OH$, is derived from the optically inactive β-carotene. It is present in the sunflower, capsicum and yellow maize.

Xanthophyll, sometimes termed *lutein*, is a dihydroxy-α-carotene, $C_{40}H_{54}(OH)_2$. It was isolated by Willstätter from leaves and the yolk of hens' eggs. Whereas carotenes are comparatively soluble in light petroleum, the hydroxy compound only dissolves readily in alcohol. Xanthophyll can therefore be extracted from the mixture, dissolved in light petroleum, by shaking with methyl alcohol which forms a separate layer.

Zeaxanthin, $C_{40}H_{54}(OH)_2$, is a pigment present in maize and egg yolk ; it accompanies *rhodoxanthin* in the berries of the yew. It is derived from β-carotene, the hydroxyl groups being probably in positions 5 and 5′ (for numbering see β-carotene). Zeaxanthin occurs as the dipalmitic ester, *physalien*.

Capsanthin, $C_{40}H_{58}O_3$, has been separated from red pepper (paprika) by chromatographic adsorption methods. It contains a terminal ketonic group and a 5-hydroxy-β-ionone ring.[1]

Astacene, $C_{40}H_{48}O_4$, the distinctive pigment of the *Crustaceæ*, has been isolated from lobster shell and characterised by Kuhn. It is also present in red goldfish and prawn, and may occur either as a chondroprotein or as an ester from which it is liberated on hydrolysis. The compound has thirteen easily reducible double bonds and is probably a 4 : 5 : 4′ : 5′-tetraketo-β-carotene, whose acid properties are due to enolisation.

Fucoxanthin, the brown pigment of brown algæ has not been fully examined. It has been given the composition $C_{40}H_{56}O_6$ [2] or $C_{40}H_{60}O_6$.[3]

Among *acidic polyenes* may be mentioned *crocetin* and *bixin*.

Crocetin, $C_{20}H_{24}O_4$, m.p. 285°, is present in the red colouring matter of saffron as the glycoside *crocin* (crocetin digentiobioside). It is a dicarboxylic acid with seven double bonds, which is represented [4] by the symmetrical formula, HOOC.CMe : **A** : CMe.COOH (for **A** see p. 824). Crocin has been shown to play an important part in the fertilisation of certain plants.

Bixin, $C_{25}H_{30}O_4$, m.p. 196°, is the yellow pigment of annalto seeds (*Bixia orellana*). It is the monomethyl ester of norbixin, a symmetrical dicarboxylic acid, and is formulated [4] as HOOC.CH : CH.CMe : **A** : CMe.CH : CH.COOMe. On ozonisation it yields β-acetylacrylic ester, $CH_3.CO.CH : CH.COOMe$. Oxidation gives four molecular proportions of acetic acid, hence there are four methyl groups linked to the polyene chain. Hydrogenation converts norbixin into perhydronorbixin, a saturated acid whose structure has been established by synthesis. Bixin was formerly used for dyeing, and is still employed for colouring foodstuffs (butter, margarine) and in the manufacture of varnishes.

[1] L. Zechmeister and L. Cholnoky, *Ann.*, 1936, **523**, 101. [2] Karrer *et al.*, *Helv.*, 1931, **14**, 622. [3] I. M. Heilbron and R. F. Phipers, *Biochem. J.*, 1935, **29**, 1369. [4] R. Kuhn and co-workers, *Ber.*, 1931, **64**, 1732 ; 1932, **65**, 1873 ; Karrer and co-workers, *Helv.*, 1932, **15**, 1399 ; 1933, **16**, 297, 337.

ANTHOCYANINS [1]

In this group are included the colouring matters of flowers and berries, which give rise to the wonderful variety of tints encountered in the vegetable kingdom.

The extracts from flowers, like the crude chlorophyll solutions obtained from leaves, contain the colouring matters admixed with highly complex substances of a colloidal nature, which render the isolation of the somewhat unstable pigments a difficult problem. Anthocyanins, however, although containing no nitrogen, possess well-marked basic properties by means of which it is possible to effect their purification. They combine with mineral and organic acids to give well-defined crystalline salts. These salts are of the oxonium type, but they are less completely hydrolysed in solution than the salts of pyrones (p. 672). Anthocyanins are also phenolic in character and thus form salts with bases.

The compounds of anthocyanins with acids are red in colour, free anthocyanins are violet, and the alkali salts are blue. Many of the variations in the colours of flowers are due to the occurrence of anthocyanins in these three states. In addition, further changes in tint may arise from variations in the concentration of the anthocyanins and of other co-pigments in the plant tissues, such as tannins and flavonols.[2] The colour of anthocyanins fades in solution as the result of structural changes.

Anthocyanins are glycosides, and when heated with 20 per cent. hydrochloric acid they are rapidly and completely decomposed into a sugar and the corresponding coloured components known as **anthocyanidins.**

Willstätter and Everest showed that a mixture of anthocyanin and anthocyanidin could be separated by shaking with a mixture of amyl alcohol and dilute acid. The glycoside is retained by the aqueous acid and the anthocyanidin passes quantitatively into the amyl alcohol.

Methods of Isolation.—In many cases anthocyanins may be isolated by extracting the flowers, or the skins of the berries, with alcohol containing hydrochloric acid, followed by precipitation of the extract with ether and recrystallisation of the crude chloride from alcoholic or aqueous alcoholic hydrochloric acid.

A second method consists in the precipitation of the anthocyanins in the form of their sparingly soluble crystalline *picrates*, a process which has also been used for isolating the vegetable alkaloids. This method was first employed in the case of the colouring matter of the grape, and has since been successfully applied to the isolation of pigments of other berries and flowers. From grape-skins it is possible to obtain in a few

[1] See *The Natural Organic Colouring Matters*, by A. G. Perkin and A. E. Everest (Longmans, Green & Co.). Willstätter, *Ber.*, 1914, **47**, 2865; *Ann.*, 1915, **408**; 1917, **412**; *Ber.*, 1924, **57**, 1938. R. Robinson, *J. C. S.*, from 1922 onwards. R. Robinson and R. Willstätter, *Ber.*, 1928, **61**, 2503. Robinson and Robinson, *Nature*, 1933, **132**, 625; 1936, **137**, 172. Hill, *Chem. Rev.*, 1936, **19**, 27. [2] For further details see Mrs G. M. Robinson, *J. A. C. S.*, 1939, 1606.

minutes the fine red crystals of the anthocyanin picrate, and these, on treatment with a methyl alcoholic solution of hydrochloric acid, are converted into the anthocyanin chloride.

Anthocyanins and Anthocyanidins—The first anthocyanin to be obtained in the form of its crystalline chloride was **cyanin,** the pigment of the cornflower.[1] In the blue flower it is present as the potassium salt.

The colouring matter of the red rose has also proved to be identical with cyanin. For preparative purposes the rose is a better starting material than the cornflower. From the dried petals it is possible to obtain approximately 1 per cent. of their weight as the crystalline cyanin chloride.

On hydrolysis cyanin decomposes into **cyanidin** and two molecules of glucose.

The colouring matter contained in the skin of the cranberry and the leaves of copper beech is known as **idæin,** and is also a derivative of cyanidin, being composed of one molecule of galactose combined with one of cyanidin.

Cyanidin has the composition $C_{15}H_{10}O_6$, and its chloride, $C_{15}H_{11}O_6Cl$.

The anthocyanin **pelargonin** present in the scarlet pelargonium is a diglucoside of the anthocyanidin **pelargonidin,** $C_{15}H_{10}O_5$, which contains one oxygen atom less than cyanidin.

The violet flowers of the delphinium (*Delphinium consolida*) contain the anthocyanin **delphinin,** which is of more complex structure. On hydrolysis it decomposes into two molecules of glucose, two molecules of *p*-hydroxybenzoic acid and one molecule of anthocyanidin. The latter, which has been named **delphinidin,** gives a chloride of the formula $C_{15}H_{11}O_7Cl$, and thus contains one atom of oxygen more than cyanidin.

Derivatives of delphinidin appear to be distributed in nature in flowers and fruit of a deep violet or blue colour. Willstätter and his co-workers have isolated four other anthocyanins, all of which are derived from methyl ethers of delphinidin.

Œnin, the colouring matter of the blue grape, and **malvin,** present in the wild mallow, are mono- and diglucosides respectively of **malvidin.** On being warmed with hydriodic acid malvidin loses two methyl groups and is converted into delphinidin, of which it is therefore a dimethyl ether.

Peonin is a diglucoside of **peonidin** and is the colouring matter of the red peony. **Hirsutin,** from *Primula hirsuta,* is a diglucoside of **hirsutidin,** containing three methyl ether groupings. **Chrysanthemin** or **asterin** is a monoglucoside of cyanin present in the scarlet aster.

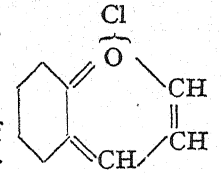
The quantities of anthocyanins present in the different parts of plants vary within wide limits. In the pelargonium and mallow, the proportion is as high as 6·5 to 7·5 per cent. of the dried flowers; in the berries, however, it is much lower, amounting, for example, to 0·4 per cent. of the dried skins of the cranberry.

[1] Willstätter and Everest, *Ann.*, 1913, 401, 1.

Constitution of the Anthocyanidins

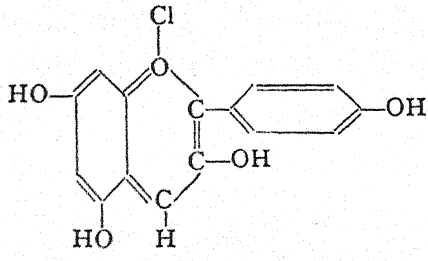
The empirical composition of the sugar-free anthocyanidins suggests that they are closely allied to the yellow mordant colouring matters so widely distributed in plants, and especially to the dye-stuffs of the flavone and flavonol series, the structure of which has been established by the analytical investigations of A. G. Perkin and others, and the syntheses of Kostanecki (see p. 674). Thus cyanidin in its neutral state is isomeric with luteolin and kampherol: pelargonidin is isomeric with apigenin and galangin: and delphinidin with quercetin and morin.

These facts, coupled with an examination of the decomposition products obtained by degradation with concentrated alkali, led Willstätter to formulate the anthocyanidins as oxonium salts derived from phenyl-benzopyrylium, or, as it is more usually termed, **flavylium.** This earlier work has been extended by that of Karrer, and more particularly by the syntheses of Robinson. There are three fundamental types of anthocyanidins, which differ in the number of hydroxyl groups present, as shown in the formulæ for **pelargonidin, cyanidin** and **delphinidin** respectively. All other anthocyanidins are methylated or acylated derivatives of one or other of these parent compounds, the most important being the mono-, di- and trimethyl ethers, **peonidin, malvidin** (*syringdin*) and **hirsutidin.** The

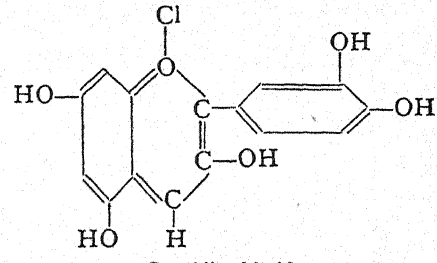


Benzopyrylium chloride

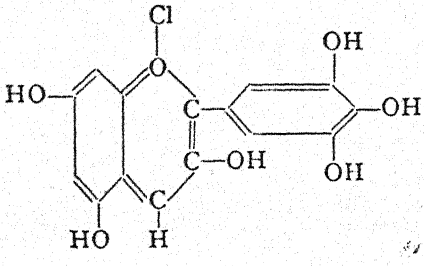
Anthocyanidins.



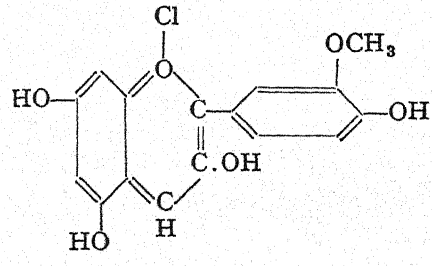
Pelargonidin chloride
(From the pelargonium)



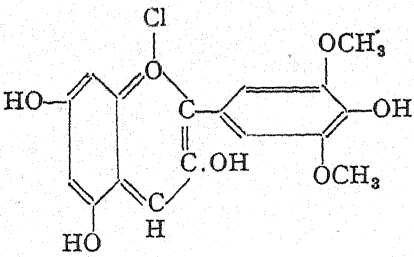
Cyanidin chloride
(From the cornflower and rose)



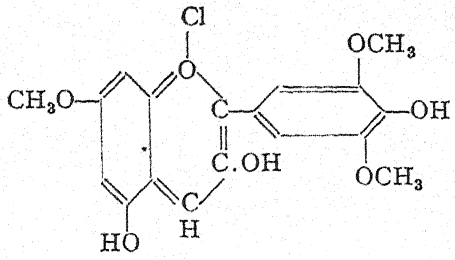
Delphinidin chloride
(From the delphinium)



Peonidin chloride
(from the red peony).

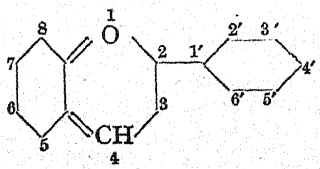


Malvidin (syringidin) chloride
(from wild mallow and grape)

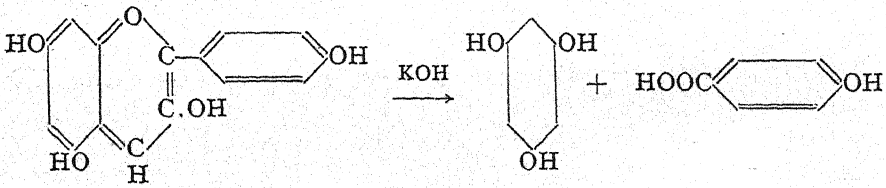


Hirsutidin chloride
(from *Primula hirsuta*).

systematic nomenclature of these compounds is based on the numbering given in the adjoining diagram, according to which cyanidin is described as 3 : 5 : 7 : 3′ : 4′-*pentahydroxy-flavylium chloride.*



Anthocyanidins, on disruption by heating with concentrated alkalis, yield two aromatic products, one of which is a phenol and the other a carboxylic acid. In this as in many other respects they resemble the flavone derivatives, a fact which has greatly facilitated the determination of their structures.



Pelargonidin — Phloroglucinol — *p*-Hydroxybenzoic acid.

Methylated anthocyanidins are best degraded by Karrer's method using hot dilute (10 per cent.) alkalis in an atmosphere of hydrogen, thus avoiding the demethylation which occurs with concentrated alkali. In this way Karrer first established the positions of the methoxy groups in peonidin, malvidin and hirsutidin.

All anthocyanidins so far investigated yield as the phenolic component either *phloroglucinol* or its *mono-methyl ether*. The second component depends on the oxygen content of the original substance :

Pelargonidin, $C_{15}H_{10}O_5$, gives p-*hydroxybenzoic acid*, $HO.C_6H_4.COOH$.

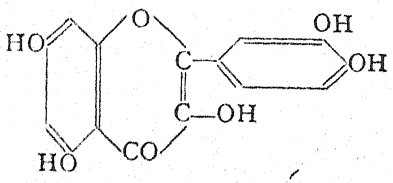
Cyanidin, $C_{15}H_{10}O_6$, gives *protocatechnic acid*, $(HO)_2C_6H_3.COOH$.

Delphinidin, $C_{15}H_{10}O_7$, gives *gallic acid*, $(HO)_3C_6H_2.COOH$.

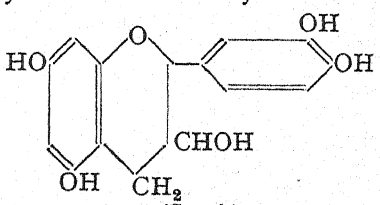
Methylated anthocyanidins with dilute aqueous alkalis yield the corresponding methyl derivatives.

The structure ascribed to cyanidin suggests that the compound could be prepared from quercetin, and that anthocyanidins in general could be obtained from flavonols. This is readily seen by comparing the above formula for cyanidin with the following one for quercetin. By reducing

quercetin with magnesium and aqueous methyl alcoholic hydrogen chloride, Willstätter and Mallison did succeed in isolating a small quantity of cyanidin. Another product obtained from natural sources, *dl-epi*catechin, of the tannin class, has been produced by the reduction of cyanidin.

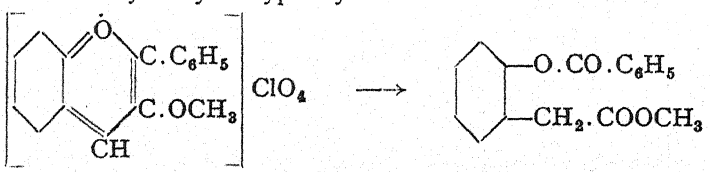


Quercetin.



*epi*Catechin

A simple reaction bearing on the structure of the heterocyclic ring was discovered by Dilthey[1] in the oxidation of 3-methoxyflavylium perchlorate with an acetic acid solution of hydrogen peroxide, which led to the rupture of the 2 : 3-double bond and the formation of the benzoyl derivative of methyl *o*-hydroxyphenylacetic ester.

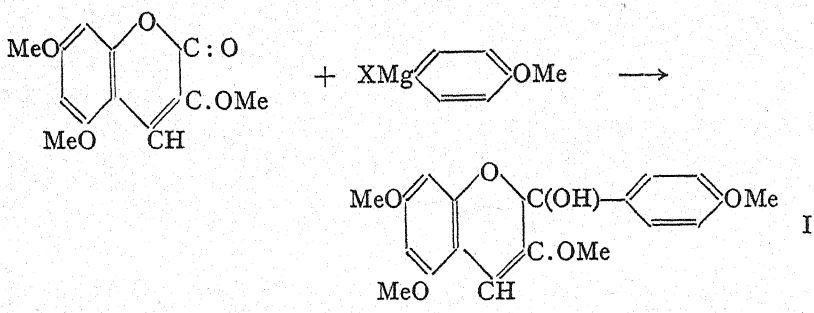


All the above transformations serve to confirm the earlier views on the general structure of anthocyanins, which has been placed on a more precise basis by synthetic work.

There still remains some uncertainty regarding the actual seat of the positive charge on the organic cation. The oxonium salt formula containing an orthoquinonoid structure and with the anion linked to quadrivalent oxygen was advanced in 1908 by Perkin, Robinson and Turner. This is in agreement with the nitration of 2-phenyl-benzoflavylium perchlorate carried out by Le Fèvre,[2] who found that the nitro group entered the meta position in the 2-phenyl nucleus to the extent of 84 per cent. Such an orientation is to be expected if the oxygen atom carries a positive charge. In some respects, however, the oxonium theory is unsatisfactory and alternative suggestions have been put forward which represent the charge as borne by the organic complex as a whole (*centric theory*) or by one of the carbon atoms, 2 or 4, of the heterocyclic ring (*carbonium* or *carbenium theories*). For a discussion of the evidence on these points see D. Hill, *Chem. Rev.*, 1936, **19**, 27.

Syntheses of Anthocyanidins and Anthocyanins.—One method is to treat coumarins with aryl magnesium halides. For example, by interaction of 3 : 5 : 7-trimethoxy-coumarin and anisyl magnesium halide Willstätter[3] prepared the carbinol base I. On being heated in a sealed tube with concentrated hydrochloric acid the methoxy groups were hydrolysed with the formation of pelargonidin chloride.[4]

[1] *Ber.*, 1931, **64**, 2082; *J. prakt. Chem.*, 1933, **138**, 42. [2] *J. C. S.*, 1929, 2771. [3] *Sitzber. preuss. Akad. Wiss.*, 1914, **29**, 402, 769; *Ber.*, 1914, **47**, 2865. [4] An extended examination of this reaction by Heilbron (see Heilbron, D. Hill and Walls, *J. C. S.*, 1931, 1701) showed that the formation of flavylium salts depends greatly on the experimental conditions and on the nature and position of substituents. 4-Substituted coumarins only give very small yields, the main product being a diaryl-Δ^3-chromene.

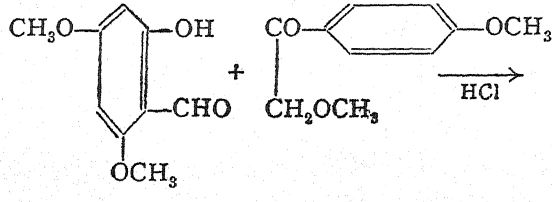


I.

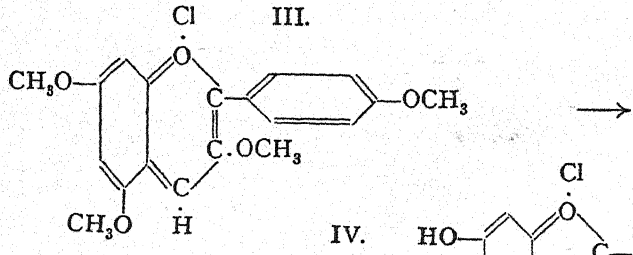
A more general method is to start from substituted *o*-hydroxybenzaldehydes and acetophenones as illustrated in the following synthesis of pelargonidin by Robinson and Pratt.[1]

2-Hydroxy-4 : 6-dimethoxy-benzaldehyde (I) and ω : 4-dimethoxyacetophenone (II) were condensed together in ethereal solution, in the presence of dry hydrochloric acid gas, to give tetramethyl-pelargonidin chloride (III). The latter was then demethylated to pelargonidin chloride (IV) by boiling with hydriodic acid in the presence of phenol.

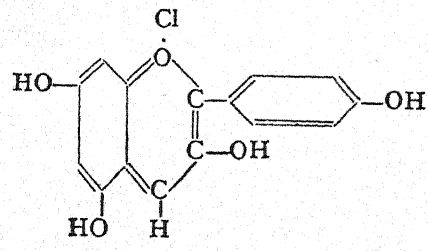
I. II.



III.



IV.

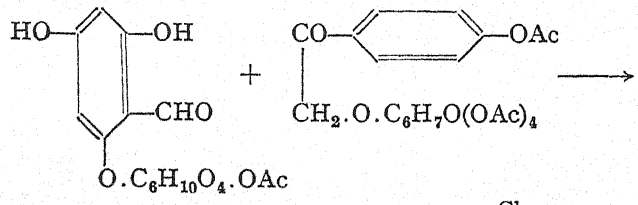


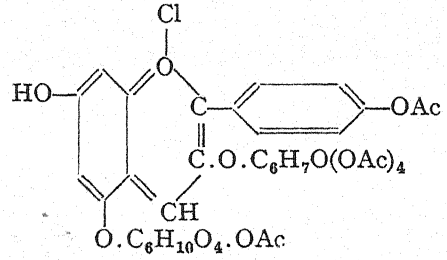
Purer products are usually obtained by protecting the hydroxyl groups by acetylation or benzoylation.

On applying similar methods to substances containing sugar residues, Robinson [2] succeeded in synthesising a number of the naturally occurring anthocyanins in such a manner as to establish their structures. Thus

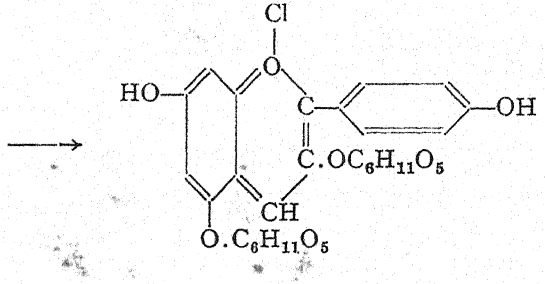
[1] *J. C. S.*, 1924, **125**, 190. [2] A. Robertson and Robinson, *J. C. S.*, 1928, 1256; Robinson and A. R. Todd, *ibid.*, 1932, 2293, 2299, 2488. Robinson and Robinson, *Nature*, 1933, **132**, 625.

pelargonin was obtained by condensing the *o*-acetylglucosidyl derivative of phloroglucinaldehyde with *ω*-*o*-tetracetyl-*β*-glucosidyl-4-acetoxyacetophenone (prepared from acetbromoglucose, *ω*-hydroxy-4-acetoxyacetophenone and dry silver carbonate in benzene) with the aid of hydrogen chloride in dry ethyl acetate. The intermediate flavylium





(I.)



(II.)

salt I, which was first formed, was allowed to stand in contact with dilute alkali in an atmosphere of hydrogen, when the protective acetyl groups were hydrolysed off. Final acidification with hydrochloric acid yielded pelargonin chloride II.

These investigations have shown that the carbohydrate is commonly united to position 3, or positions 3 and 5, of the anthocyanidin nucleus, and that the majority of these compounds may be classified as belonging to one or other of the following groups: (*a*) 3-monoglucosides and 3-monogalactosides, (*b*) 3-rhamnosides and other 3-pentoseglycosides, (*c*) 3-biosides, (*d*) 3 : 5-diglycosides and (*e*) acylated anthocyanins.

The best known and most widely occurring anthocyanins are those of group (*d*), which includes *pelargonin*, the 3 : 5-diglucoside of pelargonidin, and *cyanin*, the 3 : 5-diglucoside of cyanidin. Among the acylated derivatives of group (*e*) are *delphinin*, a *p*-hydroxybenzoylated monoglucoside of delphinidin, and *gentianin*, the corresponding *p*-hydroxycinnamoyl derivative. Further information regarding these compounds has already been given in the earlier part of this section.

XI

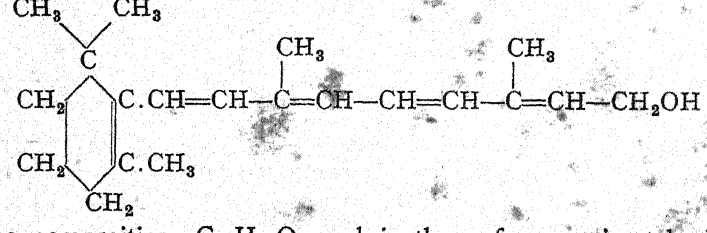
Vitamins and Hormones[1]

Vitamins and *hormones* are organic compounds of extraordinarily high physiological potency which are essential in small amounts for the well-being of all animal organisms. The distinction between the two groups is not always very clearly marked, but in general the term vitamin is used to describe principles which are already present in the active state in foodstuffs, whereas the name hormone is reserved for those which are elaborated within the organism by special glands or tissues, such as the thyroid and pituitary glands.

VITAMINS.—Only those vitamins are mentioned here the molecular constitutions of which have been at least partially established. It must be emphasised, however, that the isolation and study of these compounds represents a difficult field of research and the possibility exists that some of the less well-defined vitamins may eventually prove to be mixtures of several physiologically active products. The vitamins designated briefly by the letters A, B, C and D have been examined in considerable detail.

Vitamin A (*axerophthol*), a "fat-soluble" vitamin, is found in association with fats and is present in high concentration in the liver oils of fishes such as cod and especially halibut. It was originally discovered and studied in cod-liver oil, where it occurs in conjunction with vitamin D, another fat-soluble compound. Vitamin A promotes the growth of young animals and an adequate supply of it serves as a protection against certain types of infection. One of the earliest signs of vitamin A deficiency is night blindness; a continued lack of the vitamin may lead to hardening of the conjunctiva, corneal softening (*xerophthalmia*) and to complete blindness. Structurally, the vitamin is closely related to the carotenes of plants present in carrots and green vegetables, which can also serve as a source of the compound. In this case the provitamin or immediate precursor of the active principle is the intensely yellow polyene hydrocarbon *carotene*, $C_{40}H_{56}$ (see p. 824), which is converted into vitamin A in the liver.

The molecular structure of vitamin A has been established by the work of Karrer and of Heilbron. It is a crystalline compound, m.p. 63·64°,[2]



of the composition, $C_{20}H_{30}O$, and is thus of approximately half the molecular weight of carotene, from which it appears to be formed by

[1] Hopkins, *Nature*, 1935, 708; Pryde, *ibid.*, p. 713. [2] J. G. Baxter and C. D. Robertson, *J.A.C.S.*, 1942, 64, 2411.

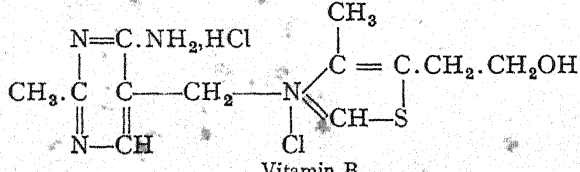
hydrolytic cleavage. The evidence is in agreement with the preceding structure, representing a highly unsaturated alcohol built up from four isoprene units and containing a β-ionone ring.

A recent discovery is the existence of a vitamin A_2 in freshwater fishes. This also appears to be formed in the organism from carotene, although its biological function is not yet known. It differs from vitamin A in its chromogenic properties, but is probably of a closely related structure.[1]

Vitamin B Group.[2]—At first thought to be represented by a single compound, this group has proved to include a number of components. Up to date the following have been isolated and examined in detail: *aneurin*, *riboflavin*, *nicotinic acid*, *pyridoxin* and *pantothenic acid*. All members of this group are soluble in water and are present in variable proportions in liver, yeast, milk and vegetables.

Vitamin B_1, *aneurin*, *thiamin*, is a thermolabile compound which is essential for the normal progress of carbohydrate metabolism. When deficiency occurs pyruvic acid and other ketonic compounds accumulate in the organism instead of undergoing further degradation, with results that may lead to beri-beri and neuritis. The antineuritic vitamin is widely distributed in natural foods, being present in the cortical parts of grain, but not in the endosperm; it is relatively abundant in yeast, where it is accompanied by other members of the B group. Cases of beri-beri among natives living on rice have been traced to loss of aneurin due to the outer surface of the grain having been removed by friction during transit. The powdery "rice-polishings" constituting this part of the grain have served as a source of the vitamin.

Aneurin has the empirical formula $C_{12}H_{18}ON_4Cl_2S$, and is the only known vitamin to contain sulphur. Its structure is as follows:

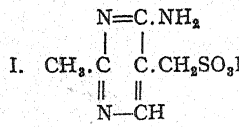


Vitamin B_1

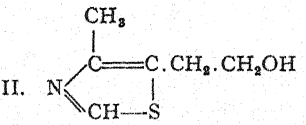
The determination of the structure is mainly due to R. R. Williams,[3] who observed that aneurin was quantitatively disrupted by aqueous sodium bisulphite into two components. One, a base, was found to be oxidisable to the known 4-methylthiazole-5-carboxylic acid and was formulated[4] as 4-methyl-5-hydroxyethyl-thiazole (II), since confirmed by synthesis.[4] Examination of the other component proved it to be a sulphonic acid derived from 4-amino-2-methyl-pyrimidine (I). The key to the exact structure of the pyrimidine fragment in aneurin was found in a diacidic base obtained from the vitamin by use of alkaline permanganate or of sodium in liquid ammonia. This has

[1] See A. E. Gillam, I. M. Heilbron, W. E. Jones and E. Lederer, *Biochem. J.*, 1938, **32**, 118. A suggested formula is that of vitamin A with an additional .CH : CH. immediately preceding the .CH_2OH group. [2] For survey, see R. D. Haworth, *Ann. Rep.*, 1937, 352; A. R. Todd, *J. C. S.*, 1941, 427. [3] *J. A. C. S.*, 1935, **57**, 229, 536. [4] H. T. Clarke and S. Gurin, *ibid.*, 1935, **57**, 1876.

been shown to be 4-amino-5-aminomethyl-2-methyl-pyrimidine (VI) by its synthesis from acetamidine by several workers.[1] Todd and Bergel obtained it by condensing

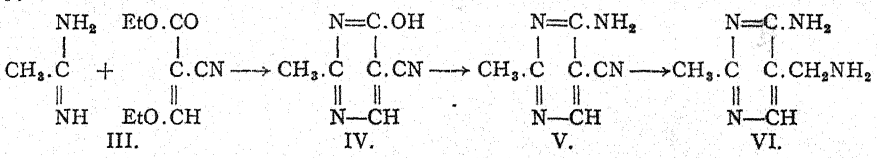


I.



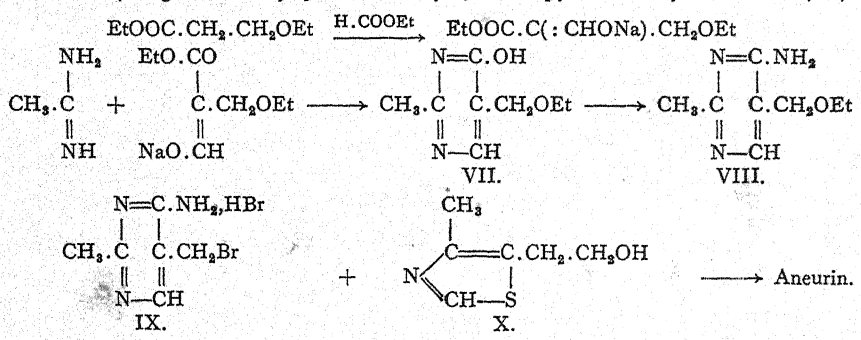
II.

acetamidine with ethyl α-ethoxymethylene-α-cyanoacetate (III) to form an intermediate compound which on being heated with alkali gave 4-hydroxy-5-cyano-2-methyl-pyrimidine (IV). This last compound was refluxed with phosphoryl chloride (OH ⟶ Cl) and treated with ammonia (Cl ⟶ NH_2), yielding 4-amino-5-cyano-2-methyl-pyrimidine V, which on catalytic reduction was converted into 4-amino-5-aminomethyl-2-methyl-pyrimidine (VI).



III. IV. V. VI.

These preliminary investigations were rapidly followed by several syntheses of aneurin itself,[2] those of Williams in America and Grewe in Germany being on very similar lines. Williams's method, which has been used on a large scale, is as follows: β-ethoxy-propionic ester reacts with ethyl formate in the presence of sodium ethoxide to give ethyl sodioformyl-β-ethoxy propionate, which is condensed with acetamidine to form 2-methyl-5-ethoxymethyl-4-hydroxy-pyrimidine (VII). The hydroxyl group in the latter is replaced successively by Cl and NH_2 by use of phosphorus oxychloride followed by ammonia, and the resulting compound (VIII) heated with hydrogen bromide (OEt ⟶ Br) to give 2-methyl-5-bromomethyl-4-amino-pyrimidine hydrobromide (IX).



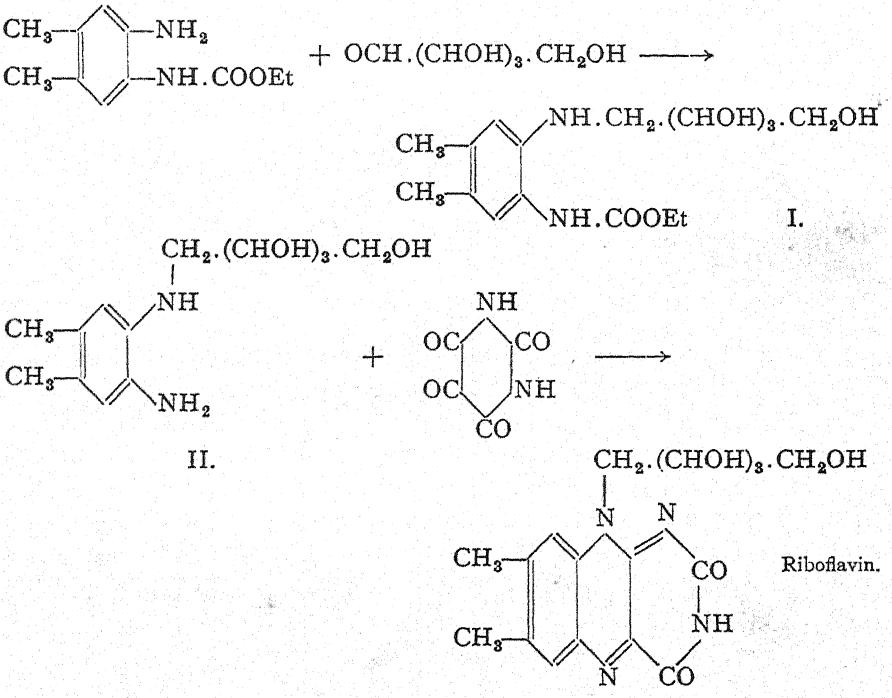
VII. VIII. IX. X.

In the final stage the bromocompound IX is heated for a short time with 4-methyl-5-β-hydroxyethyl-thiazole (X, see above) to form the hydrobromide of vitamin B_1 in good yield. When converted into the hydrochloride the synthetic vitamin had the same physiological activity as the natural product.

The pyrophosphoric ester of aneurin is the co-enzyme of carboxylase which is essential for the breakdown of pyruvic acid in the body, and which also takes part in alcoholic fermentation.

[1] A. R. Todd and F. Bergel, *J. C. S.*, 1937, 364; R. Grewe, *Z. physiol. Chem.*, 1936, **242**, 89; Andersag and Westphal, *Ber.*, 1937, **70**, 2035. [2] Cline, Williams and Finkelstein, *J. A. C. S.*, 1937, **59**, 1052; Todd and Bergel, *J. C. S.*, 1937, 1504; Andersag and Westphal, *loc. cit.*

Vitamin B_2, *riboflavin*, *lactoflavin*,[1] is a growth-promoting factor which remains with the other thermostable members of the B group after vitamin B_1 has been destroyed by heating in an autoclave. It was discovered mainly through the work of Kuhn, György and Wagner-Jauregg [2] on a yellow pigment obtained from whey, which was identified with vitamin B_2. The structure of this compound, riboflavin, was established by the researches of Kuhn and of Karrer. The latter [3] effected the first complete synthesis, starting from an equimolecular mixture of 1-amino-2-carbethoxyamino-4 : 5-dimethylbenzene and *d*-ribose, which was hydrogenated in the presence of nickel to form 2-carbethoxyamino-4 : 5-dimethyl-phenylribamine (I). This compound was hydrolysed by alkali to 2-amino-4 : 5-dimethyl-phenylribamine (II), followed by condensation with alloxan in acid solution. The resulting 6 : 7-*dimethyl*-9-*d*-*ribityl-isoalloxazin*, was identical with riboflavin.



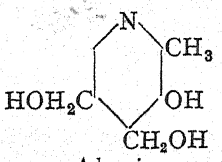
Riboflavin is a yellow crystalline compound, m.p. 298°, which is soluble in water to a yellow-green fluorescent solution. Among the best sources are yeast, vegetables, milk and liver. The phosphoric ester of riboflavin, esterified in position 5 of the ribose group, is present in Warburg's yellow respiration enzyme, and has been prepared from riboflavin.

Nicotinic acid is the anti-pellagra [4] vitamin. It has been isolated from yeast and rice, where it is accompanied by other members of the B

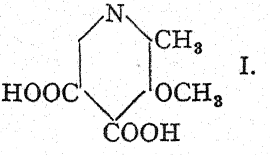
[1] Also known in America as Vitamin G. [2] *Ber.*, 1933, **66**, 1034. [3] *Helv. Chim. Acta*, 1935, **18**, 69, 522. Other syntheses have been carried out by Kuhn, *e.g. Ber.*, 1934, **67**, 1939.
[4] Pellagra is a disease involving serious skin lesions.

complex, and also in the form of **nicotinamide** from heart, muscle and liver.

Vitamin B_6, *adermin*, pyridoxin, has been found to be specific against rat dermatitis. Researches carried out in the Merck laboratories [1] in America and by R. Kuhn [2] in Germany have shown it to be a relatively simple derivative of pyridine, namely 2-methyl-3-hydroxy-4 : 5-di-(hydroxymethyl)-pyridine. The vitamin was isolated from rice bran as the hydrochloride of a weak tertiary base, $C_8H_{13}O_3N$, which was found to contain one C-methyl group, one phenol group (methylated by diazomethane) and two primary alcohol groups. The absorption spectrum classed it as a 3-hydroxy-pyridine. Oxidation with alkaline permanganate converted the methylated vitamin into a methoxy-picoline dicarboxylic acid I, the absorption spectrum of which strongly resembled that of 2 : 6-dimethyl-cinchomeronic acid. The acid also gave the fluorescein reaction, and was therefore concluded to have the carboxyls in adjacent positions. Decarboxylation with lime converted the acid into a hydroxypicoline, the picrate of which melted at 147° to 148° and was thus not that of 3-hydroxy-5-methyl pyridine, m.p. 201° to 202°, but presumably of the isomeric 2-methyl derivative. Finally, the vitamin in alkaline solution gave a blue colour with 2 : 6-dichloro-quinone-chloroimide, indicating that the para position to the phenolic group is unsubstituted.[3] In this way the above formula was deduced, and was later confirmed by syntheses.[1, 2]

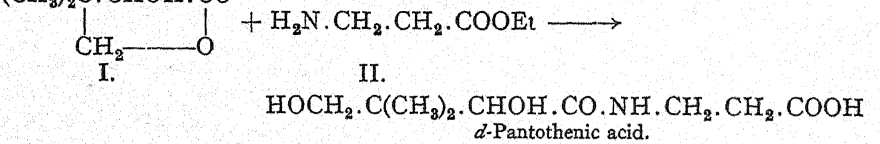


Adermin.



I.

Pantothenic Acid.—In 1933 R. J. Williams found that extracts from a very wide range of biological tissues contained a material having a remarkable stimulating effect on the growth of yeast. The active principle was later isolated from liver and was termed pantothenic acid (*Greek*: from everywhere). Further examination showed it to be identical with the "chick-dermatitis factor" and to be of importance in animal nutrition. As the result of brilliant micro-chemical investigations,[4] the vitamin has been



characterised as *N-(αγ-dihydroxy-ββ-dimethyl-butyryl)-β-aminopropionic acid.* This structure was confirmed by a synthesis, based on the con-

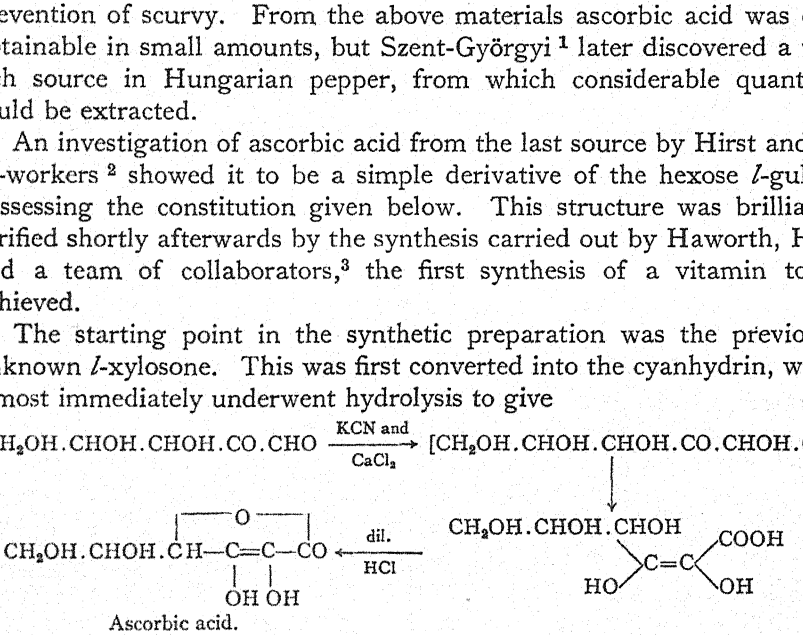
[1] E. T. Stiller, Keresztesy and Stevens, *J. A. C. S.*, 1939, **61**, 1237; S. A. Harris, Stiller and K. Folkers, *ibid.*, p. 1242; Harris and Folkers, *ibid.*, p. 1245. [2] Kuhn and co-workers, *Ber.*, 1939, **72**, 305, 309, 310. [3] Gibbs, *J. Biol. Chem.*, 1927. **72**, 649; see also Theriault, *Ind. Eng. Chem.*, 1929, **21**, 343. [4] See R. J. Williams and R. T. Major, *Science*, 1940, **91**, 246; E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy and K. Folkers, *J. A. C. S.*, 1940, **62**, 1785; R. J. Williams, H. K. Mitchell, H. H. Weinstock and E. E. Snell, *ibid.*, p. 1784.

densation at 70° of its component parts, *l*-α-hydroxy-ββ-dimethyl-γ-butyrolactone (I) and the ethyl ester of β-alanine (II), followed by removal of the ethyl groups by use of cold baryta.

Vitamin C, *l*-Ascorbic Acid.—In 1928 a highly reactive crystalline acid, $C_6H_8O_5$, was isolated by A. Szent-Györgyi from a number of sources including adrenal cortex, cabbages and oranges. This compound possessed strong antiscorbutic properties and was subsequently named *ascorbic acid*. It was quickly realised that it might prove to be the hitherto unidentified vitamin C, a component of food which is essential for the prevention of scurvy. From the above materials ascorbic acid was only obtainable in small amounts, but Szent-Györgyi [1] later discovered a very rich source in Hungarian pepper, from which considerable quantities could be extracted.

An investigation of ascorbic acid from the last source by Hirst and his co-workers [2] showed it to be a simple derivative of the hexose *l*-gulose, possessing the constitution given below. This structure was brilliantly verified shortly afterwards by the synthesis carried out by Haworth, Hirst and a team of collaborators,[3] the first synthesis of a vitamin to be achieved.

The starting point in the synthetic preparation was the previously unknown *l*-xylosone. This was first converted into the cyanhydrin, which almost immediately underwent hydrolysis to give



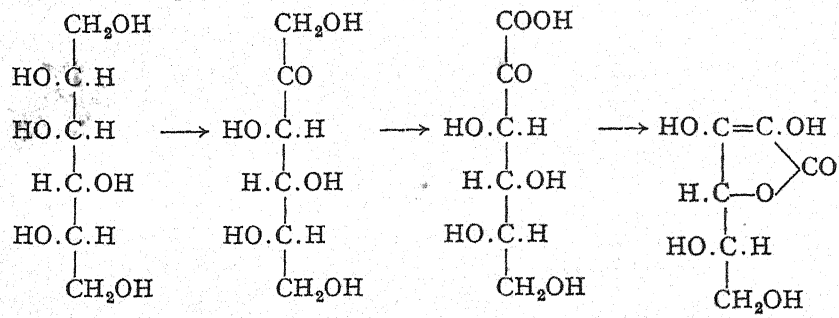
Ascorbic acid.

the corresponding keto-acid (written above in its enolic form). The latter, in the presence of dilute hydrochloric acid was transformed quantitatively into *l*-ascorbic acid, identical with the natural vitamin. *d*-Ascorbic acid was also prepared from *d*-xylosone, but was found to display little or no physiological activity.

In larger quantities *l*-ascorbic acid may be prepared from *d*-glucose [4] in the following steps. *d*-Glucose is reduced by catalytic hydrogenation to *d*-sorbitol, which is converted into *l*-sorbose by the action of the oxidising organism, *Bacterium xylinum*. *l*-Sorbose is heated under carefully controlled conditions with nitric acid, oxidising it to 2-keto-*l*-gulonic acid. The latter is not isolated but is esterified by heating it with methyl alcohol, and on subsequent treatment with sodium methoxide the

[1] I. Banga and A. Szent-Györgyi, *Biochem. J.*, 1934, **28**, 1625. [2] R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. W. Reynolds and F. Smith, *J. C. S.*, **1933**, 1270. [3] W. N. Haworth and E. L. Hirst, *J. C. S. I.*, 1933, **52**, 645; R. G. Ault, D. K. Baird, H. C. Carrington, W. N. Haworth, R. Herbert, E. L. Hirst, E. G. V. Percival, F. Smith and M. Stacey, *J. C. S.*, **1933**, 1419. [4] W. N. Haworth, *Nature*, 1934, **134**, 724. See also T. Reichstein and A. Grüssner, *Helv. Chim. Acta*, 1934, **17**, 311.

ester yields the sodium salt of ascorbic acid. This process is a rapid and cheap means of production.



d-Sorbitol — *l*-Sorbose — 2-Keto-*l*-gulonic acid — *l*-Ascorbic acid.

The accepted structure of ascorbic acid is in agreement with its chemical properties, bearing in mind the possibilities of the molecule to undergo keto-enolic change. The acid gives a quantitative yield of furfuraldehyde when boiled with hydrochloric acid ; it forms a diphenylhydrazone (ketonic structure) and gives an intense coloration with ferric chloride (enolic structure). Schiff's reagent produces no coloration, thus indicating the absence of a free aldehyde group. The most characteristic reaction, and one which is closely related to its biological activity, is the ease with which it undergoes reversible oxidation to *dehydroascorbic acid*, when the group C(OH) = C(OH) present in the ring is dehydrogenated to CO—CO. In this way Vitamin C is believed to regulate the oxidation-reduction processes of the living cell, aiding cellular respiration by acting as a hydrogen transporter. In addition to its anti-scorbutic activity the vitamin assists the body to withstand bacterial infection and toxins.

l-Ascorbic acid is contained in most fresh foods, and especially in fruit and green vegetables, in amounts which vary greatly with the species. As already stated it occurs in considerable proportions in Hungarian pepper. The compound is less stable than the other known vitamins, and is destroyed when the foods in question are heated, dried or even kept for long periods.

Vitamin D, which may exist naturally in more than one form, is a specific against rickets. It is essential for the absorption of phosphorus and calcium from the intestine and thus for maintaining the normal calcium and phosphorus levels in the body. It is present in high concentrations in fish liver oils, the most potent being those from the percomorph family, *e.g.* mackerel. Halibut and cod-liver oils are used medicinally.

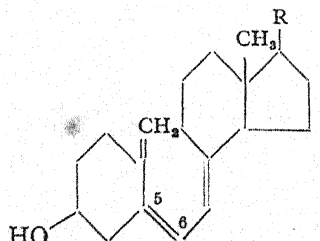
The probable structure of the natural vitamin known as D_3 has been deduced through researches on the synthetic antirachitic **vitamin D_2,** *calciferol,* with which it was for a time believed to be identified. The discovery of calciferol arose directly out of studies on the etiology of rickets. It was found that the disease could be cured by irradiating the

patient with sunlight or ultraviolet light, and later that beneficial results were also obtained by irradiating the food consumed by the patient. Further investigation showed that irradiation converts an otherwise inactive substance present in the food and tissues into a powerfully antirachitic compound. This inactive precursor was traced to the fats and eventually to ergosterol, largely owing to the work of Rosenheim and Webster, and of Hess and Windaus.

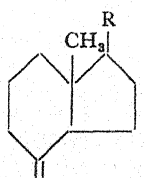
On irradiation, ergosterol undergoes a series of isomeric changes which may be summarised as follows :—

Ergosterol → lumisterol → tachysterol → calciferol → suprasterols and toxisterol.

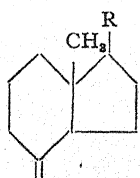
From this mixture crystalline calciferol (m.p. 115° to 117°, $[\alpha]_D$ +103° in alcohol) was isolated independently by Askew and co-workers [1] and by Windaus.[2] The molecular structure of calciferol has been deduced by oxidative degradation and from the properties of its maleic anhydride adduct. The formula shown, which was advanced by Heilbron,[3] represents



Calciferol
(R=CHMe.CH:CH.CHMe.CHMe$_2$)



I.



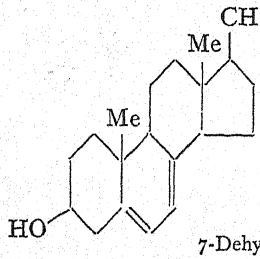
II.

the steroid nucleus as having undergone disruption in ring B, and has a methylene group attached to C_{10} in conjugation with the double bond at 5 : 6. Oxidation [3] of calciferol with cold chromic acid gave an oily unsaturated aldehyde I ; by use of permanganate the ketone II was obtained. The presence of the methylene group is supported by the production of formaldehyde on ozonisation, although it may be noted that ergosterol also yields a small quantity of formaldehyde under these conditions. Maleic anhydride forms an adduct by union with the conjugated system composed of the methylene group and the 5 : 6-double bond.

Biochemical assays showed that the ratio of rat : chick curative dose found for calciferol was not the same as that for concentrates of natural vitamin D_3. The two compounds are therefore not identical as was assumed earlier. Further search for the provitamin led in 1936 to the discovery that *7-dehydrocholesterol* (formula as for cholesterol, but with an additional double bond at 7 : 8) on irradiation gives an antirachitic compound [4] with the same biochemical assay as was found for concentrates

[1] *Proc. Roy. Soc.*, 1930, **107B**, 76 ; 1931, **108B**, 340 ; 1932, **109B**, 488. [2] *Ann.*, 1931, **489**, 252 ; 1932, **492**, 226. [3] Heilbron, R. N. Jones, K. M. Samant and F. S. Spring, *J. C. S.*, 1936, 905. Heilbron and F. S. Spring, *Chem. and Ind.*, 1935, 795. [4] Windaus, Lettré and Schenck, *Ann.*, 1935, **520**, 98 ; Windaus, Schenck and Werder, *Z. physiol. Chem.*, 1936, **241**, 100.

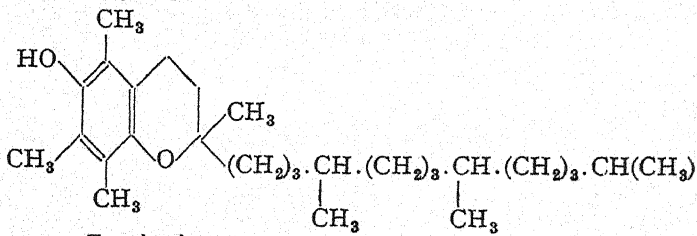
of the natural vitamin D_3. By analogy with calciferol, vitamin D_3 is therefore represented by a formula differing from that of calciferol only in having the typical cholesteryl substituent, C_8H_{17}, attached to position 17.



7-Dehydrocholesterol.

Subsequently the natural vitamin D_3 was isolated for the first time by Brockmann,[1] using chromatographic adsorption on aluminium oxide, the sources being tunny liver oil and halibut liver oil. A comparison of the 3 : 5-dinitrobenzoate with that obtained from the irradiation product of 7-dehydrocholesterol showed them to be identical. The belief that 7-dehydrocholesterol is the actual provitamin is strengthened by the discovery of Windaus[2] that this compound is present in the sterol mixture obtained from pigskin, which was already known to be rich in provitamin.

Vitamin E, the antisterility vitamin, is necessary alike for fertility of the male and the birth processes of the female. It is a fat-soluble compound which is present in the oils from wheat-germ and rice-germ and in certain other vegetable oils. From these sources have been isolated three hydroxy-compounds,[3] the α-, β- and γ-**tocopherols,** of the formulae $C_{29}H_{50}O_2$, $C_{28}H_{48}O_2$ and $C_{28}H_{48}O_2$ respectively. The oily vitamins yield crystalline allophanic esters and *p*-nitrophenyl-urethanes. Determination of their structure is due to the preliminary work[4] of Fernholz and of John, and to independent syntheses carried out in the laboratories of Karrer,[5] Todd[6] and Smith.[7] They are formulated as derivatives of chromane, α-tocopherol having three methyl groups in the benzene nucleus and β and γ-tocopherols only two. In the β-compound these methyls are in the para position to one another; in the γ-compound they are situated on the same side of the hydroxyl group.

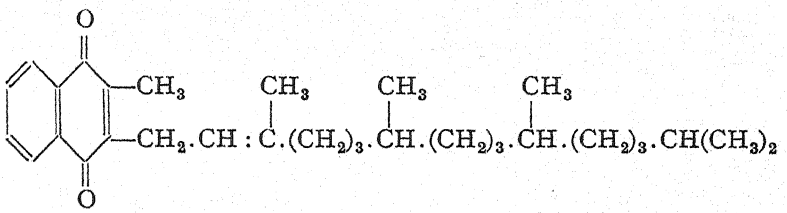


α-Tocopherol

Vitamin K_1 is the coagulation vitamin, deficiency of which leads to a

[1] *Z. physiol. Chem.*, 1936, **241**, 104, 129; 1937, **245**, 96. *J. A. C. S.*, 1936, 2155. [2] *Ibid.*, 1937, **245**, 168. [3] H. M. Evans, O. H. Emerson and G. A. Emerson, *J. Biol. Chem.*, 1936, **113**, 319. [4] E. Fernholz, *J. A. C. S.*, 1937, **59**, 1154; 1938, **60**, 700. W. John, *Z. physiol. Chem.*, 1937, **250**, 11. [5] *Helv. Chim. Acta*, 1938, **21**, 520, 820; *Nature*, 1938, **141**, 1057. [6] F. Bergel, A. Jacob, A. R. Todd and T. S. Work, *Nature*, 1938, **142**, 36. [7] L. I. Smith, H. E. Ungnade and W. W. Prichard, *Science*, 1938, **88**, 37. For a recent survey by Smith see *Chem. Rev.*, 1940, **27**, 287.

prolongation of the clotting time of the blood and to hæmorrhage. It is present in alfalfa and other green leafy tissue (cabbage, spinach) and to a lesser extent in tomato oil. The work of Doisy, Almquist and Fieser has shown the compound to be 2-methyl-3-phytyl-1 : 4-naphthaquinone.

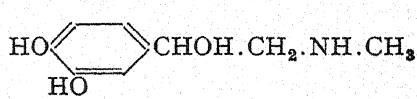


Vitamin K_1

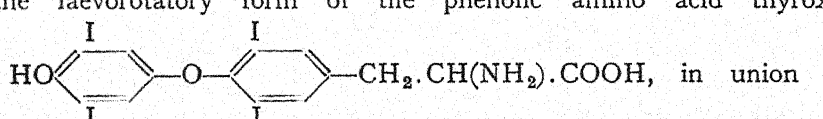
The synthetic compound prepared by Fieser [1] from 2-methyl-1 : 4-naphthahydroquinone and phytol proved to be identical with the natural vitamin K_1 from alfalfa concentrates. A second compound of this type, **vitamin K_2**, is believed to have a difarnesyl group [2] in place of the phytyl group in K_1.

HORMONES.—As has already been indicated, hormones are principles which are elaborated within the organism for the control or promotion of specific physiological processes. From the chemical standpoint most of our knowledge of the hormones is of comparatively recent date, although one of these compounds, adrenaline, has been known for a number of years.

Adrenaline, $C_9H_{13}O_3N$, is the hormone of the adrenal gland which brings about increase in the blood pressure. The natural product is a laevorotatory catechol derivative of the annexed formula. The physiologically less active racemic compound has been synthesised in the following stages. Catechol was heated with chloracetic acid in the presence of phosphorus oxychloride to form chloroacetocatechol, $(HO)_2C_6H_3.CO.CH_2Cl$. On treatment with methylamine this was converted into $(HO)_2C_6H_3.CO.CH_2.NH.CH_3$, which on reduction of the keto group to CHOH gave racemic adrenaline.[3] Natural laevorotatory adrenaline has about fifteen times the physiological activity of the dextro form.



Thyroxine.—The active principle of the thyroid gland contains the laevorotatory form of the phenolic amino acid thyroxine,



d-3 : 5-di-iodotyrosine. Racemic thyroxine was first isolated from

[1] *J. A. C. S.*, 1939, **61**, 3467. [2] S. B. Binkley, R. W. McKee, S. A. Thayer and E. A. Doisy, *J. Biol. Chem.*, 1940, **133**, 721. [3] Stolz, *Ber.*, 1904, **37**, 4149. H. D. Dakin, *Proc. Roy. Soc.*, 1905, **B 76**, 491, 498.

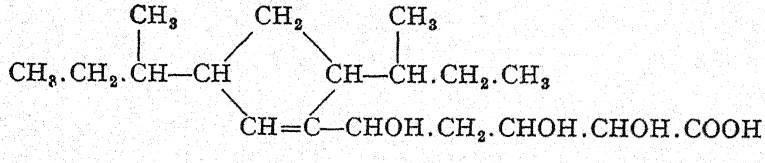
the gland by Kendall ; its structure was established later by the brilliant synthesis carried out by Harington and Barger.[1] A deficiency of thyroid secretion may lead to the diseases cretinism and myxœdema.

Secondary Sex Hormones.—The remarkable progress made in the study of this biologically important group has already been described in connection with the chemistry of the closely related sterols and bile acids (see p. 592).

Phytohormones are those naturally occurring substances which regulate the growth of plants, *e.g.* the lengthening of the cells. Such active compounds occur in the tips of seedlings, although in amounts too small to be isolated. It was noted, however, that urine had a marked effect on the elongation of young plant cells, and this observation led in 1934 to the isolation from it of **auxin-*a*** and **auxin-*b*** by Kögl.[2] These products are very probably identical with the growth-promoting compounds present in the tips of oat seedlings. Both auxins can be isolated from various vegetable oils and from malt, so that their occurrence in urine presumably arises from the inclusion of such sources in human food. It is curious that another compound obtained from urine, *β-indolylacetic acid*, is also highly active in promoting the growth of oat tips, but this cannot be described as a phytohormone as it almost certainly does not occur in the plant.

The deduction of the structure of auxin-*a* by Kögl from only 350 mg. of material is a remarkable achievement. His main points are as follows : (*a*) Auxin-*a* is a monobasic acid containing three hydroxyl groups. (*b*) With alcoholic hydrogen chloride it yields a lactone, $C_{18}H_{30}O_4$. (*c*) It is laevorotatory and undergoes mutarotation due to lactone formation. Equilibrium is reached in 1 to 2 hours, which suggests a δ-lactone structure as γ-lactones require much longer (see p. 301). (*d*) Catalytic hydrogenation adds on two atoms of hydrogen, saturating a double bond to form an acid, $C_{18}H_{34}O_5$. (*e*) Treatment with alkaline permanganate ruptures the double bond and also oxidises away five carbon atoms, leaving a dibasic acid, $C_{13}H_{24}O_4$, which contains no hydroxyl groups but yields an anhydride.

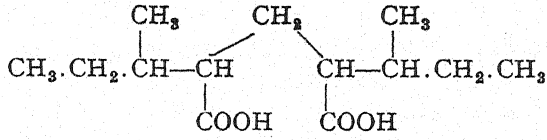
From these and other facts auxin-*a* is formulated as



Auxin-*b* has $CHOH.CH_2.CO.CH_2.COOH$ in place of the closely related group attached to the bottom right-hand carbon of the ring in

[1] Harington and Barger, *Biochem. J.*, 1927, **21**, 169. See also *Some Applications of Organic Chemistry to Biology and Medicine*, by G. Barger (M'Graw-Hill Book Co., New York, 1930). [2] Kögl, *Zeit. physiol. Chem.*, 1934, 228.

the above formula. The oxidation product mentioned under (*e*) is *aa'*-di-*sec*-butyl-glutaric acid, the constitution of which has been confirmed



by synthesis (Kögl, 1938). A structure such as auxin-*a* contains seven asymmetric carbon atoms and therefore exists in no less than 128 optical isomers. Hence it is not to be expected that the compound will be easily synthesised.

ENZYMES

At the present time it is no easy task to give an exact definition of the enzymes. Perhaps the most satisfactory description is that of Bredig, who defines them as catalytic substances which are elaborated by living organisms and are indispensable for the operation of their chemical processes. This definition applies in the case of many enzymes, although Willstätter has recently again emphasised the fact that all enzymes cannot be classed as catalysts. In general, a chemical process may be described as an enzyme reaction when it proceeds more rapidly under the influence of a preparation obtained from living cells than without the addition of the active preparation, the reactions being otherwise carried out under similar conditions.

For example, ethyl butyrate in aqueous solution is after a definite time hydrolysed to a measurable extent. If the solution is treated with a glycerine extract of the pancreas, the same degree of hydrolysis is attained in a much shorter time, although the addition of a *boiled* glycerine extract does not materially influence the rate of hydrolysis. Consequently fresh pancreas extract must contain an agent capable of greatly increasing the velocity of hydrolysis, *i.e.* an ester-splitting enzyme. Particular importance is attached to the condition that an enzyme preparation must be free from living cells. From this it follows that an enzyme is a lifeless physico-chemical system, the activity of which depends entirely on physico-chemical forces and which may therefore be investigated by purely physico-chemical methods. Although more and more biochemical processes are now being recognised as enzyme reactions, in the majority of individual metabolic changes the enzymatic character of the action has not yet been proved. The nonenzymatic changes of metabolism only proceed (within the narrow limits of temperature, acidity, etc., obtaining in the organism) under the influence of living cells. As an example may be mentioned the deamination of amino-acids which occurs on a considerable scale in living animals. Although liver freshly removed from the animal is capable, when artificially supplied with blood, of transforming alanine into lactic acid, liver tissue which has been mechanically subdivided or subjected to extraction processes no longer exhibits this property.

Detection of Enzymes.—From the above definition of enzymes it follows that they can only be recognised by means of their catalytic influence. Nevertheless, during recent years great progress has been made in our knowledge of individual enzymes. O. Warburg has employed photochemical methods in studying the absorption spectrum of a respiratory ferment and thus demonstrated its close chemical relationship to hæmatin. These investigations have for the first time permitted a glimpse into the structure of an enzyme.

In many enzyme reactions the catalytic influence as measured by the velocity constant is largely proportional to the quantity of added enzyme preparation. This observation can hardly be interpreted otherwise than on the assumption that the enzymes themselves represent substances, the relative amount of which can under certain conditions be measured quantitatively by its catalytic activity. Quantitative methods of estimating yields of enzymes play a considerable rôle in modern preparative chemistry. They provide a means of determining the degree of purity of a particular preparation and form the basis of analytical investigations of the purified product. The results obtained are, however, somewhat limited since they only show that in the cases so far examined enzymes may be progressively freed from all known compounds without losing their activity.

Preparation of Enzymes.[1]—The first step in the preparation of an enzyme is to separate it from living cells. This stage can often be avoided if a biological fluid, especially an active secretion such as gastric or intestinal juice, be employed as starting material; but owing to the troublesome operations necessary for the production of pure secretions this type of work is restricted almost entirely to the digestive juices, which however contain a mixture of enzymes in a form unsuited to exact investigation. Nowadays researches on the digestive juices rarely make use of the corresponding secretion as starting material; the sole possible means of preparing those enzymes which induce a deep-seated decomposition of biological substances is the extraction of the finely divided organ under consideration. An important method is that due to E. Buchner in which the cells are disrupted by pulverising the organ with quartz sand and kieselguhr. The juice containing the ferments is then pressed out from the mixture under 300 atmospheres pressure. This treatment does not merely consist in the simple disruption of the cell membranes, but in all probability complicated adsorption processes come into play.

As is to be expected from the complexity of the biochemical reactions taking place in living organisms, the extracts obtained in this manner always consist of a mixture of different enzymes. From these extracts

[1] Reference may be made to the following works: W. M. Bayliss, *The Nature of Enzyme Action* (Longmans, Green & Co., 1925). C. Oppenheimer, *Die Fermente und ihre Wirkungen* (5th edition, Thieme, Leipzig, 1929); also, *Lehrbuch der Enzyme* (Thieme, 1927). H. v. Euler, *Chemie der Enzyme* (J. Bergmann, Munich and Wiesbaden, 1922-27). E. Waldschmidt-Leitz, *Die Enzyme* (J. Vieweg, Brunswick, 1926). A. Foder, *Das Fermentproblem* (Steinkopf, Dresden, 1929). J. B. S. Haldane, *Enzymes* (Longmans, Green, 1930).

attempts are then made to remove impurities and other enzymes as completely as possible from the active substance, for which purpose use is made of adsorption, elution, salting out and other reversible processes and dialysis, only mild experimental conditions being employed. Stable dry preparations may often be successfully prepared by precipitation with alcohol or acetone and washing the precipitate with ether, although many enzymes lose much of their activity under this treatment.

Specific Influence of Enzymes.—The most noteworthy property of an enzyme is the specific nature of its reactions, which is frequently so strongly developed that the activity is exhibited solely towards one particular substance, known as the *substrate* of the enzyme. Extremely small modifications in the molecular structure of the substrate are sufficient to render it immune from attack. The fact that asymmetric substances in nature usually occur in the active and not in the racemic forms, finds one explanation in the preferential action of synthetic and disruptive enzymes on one of the two active isomerides of the asymmetric compound. Yeast, for example, is only able to ferment *d*-glucose; the laevorotatory sugar is not attacked.

The more carefully enzymes are studied, the finer are the degrees of specificity discovered, and the more certain becomes the conviction that many closely related reactions which have hitherto been ascribed to the catalytic activity of one and the same enzyme are in reality the result of several distinct enzymes. The same power of selectivity which determines the most complex functions of the organism may also be traced in the individual chemical processes of the living cell itself. Hence enzyme chemistry is of fundamental importance for the study of life processes.

The specific character of the enzymes, the importance of which for our knowledge of biological processes has been indicated above, has proved of great service in chemistry and medicine. Reference may be made to the biochemical method for the resolution of racemic compounds, to the use of enzymes in the classification of α- and β-glucosides, and to the simple quantitative micro-chemical determination of urea by means of urease.

Properties of Enzymes.—In a book of this kind space can only be found for a few general remarks on the properties of enzymes. Almost all the members of this class are very sensitive towards physical and chemical change. Heating for a short time above 50° leads in most cases to destruction, as does also treatment with the stronger alkalis, acids and salts of many of the heavy metals. Above all, the optimum conditions of reactivity of enzymes are subject to very sharp limitations, as may be seen in the pronounced dependence of enzyme action upon the acidity of the medium, which is so characteristic as to be employed for differentiating between closely related enzymes. The optimum acidity for almost all enzymes lies, like the reaction of most of the body fluids, not very far from the neutral point. An exception to this statement is found in the

pepsinases, including the protein-disrupting ferment of the gastric juice which normally exists in the presence of hydrochloric acid.

For the exercise of their specific influence many enzymes require activation by particular compounds which in some cases (*e.g.* amylase) may be simple salts, and in others (*e.g.* trypsin, a protein-splitting enzyme of the pancreas) are represented by complex products.

Certain enzymes or enzyme systems such as **invertase, maltase** and **zymase** have already been discussed in some detail in connection with alcoholic fermentation. A brief reference is made in the following paragraphs to other enzymes of importance.

Pepsin, a proteolytic enzyme, is secreted in the form of an inactive precursor *pepsinogen* by cells in the mucous lining of the stomach. It becomes activated in the presence of the hydrochloric acid of the gastric juice and is then capable of effecting the hydrolytic disruption (digestion) of proteins to proteoses and peptones.

Rennin, a milk-clotting enzyme, also exists in gastric juice. Apparently its sole function is to curdle milk, the curd being subsequently attacked by the pepsin present.

Trypsin is secreted by the pancreas in the form of an inactive precursor *trypsinogen.* The latter develops an intense activity in the presence of small quantities of another enzyme **enterokinase,** which occurs in the intestinal juice. Trypsin attacks the great majority of proteins and also proteoses and peptones, degrading them to the polypeptide stage.

Erepsin, an enzyme found in the small intestine, converts proteoses and peptones in an alkaline medium into amino-acids.

Lipase occurs in the pancreatic juice and in certain plant sources. It is a fat-hydrolysing enzyme, which is only partially active when secreted by the pancreas, but exerts its full activity in the presence of the bile salts.

Amylases or **diastases,** which exist in saliva, pancreas, liver and also in germinating seeds, bring about the decomposition of starch and glycogen to maltose. These enzymes require the presence of certain neutral salts in order that their activity may be developed.

Urease is a crystalline enzyme found in *soya bean* and the seeds of other leguminosæ. It effects the hydrolysis of urea to ammonia and carbon dioxide, and is employed in the quantitative estimation of urea.

Ptyalin, secreted by the salivary glands, breaks down starch to maltose.

Various other enzymes are found in plant and animal tissues generally, and play an important part in metabolic changes. Among these are **catalases** which decompose hydrogen peroxide into water and oxygen; **oxidases,** which catalyse certain oxidative reactions; and *de-aminising enzymes.*

XII

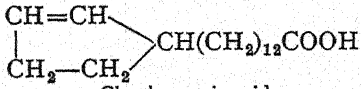
Recent Developments in Chemotherapy

Chemotherapy, or the treatment of parasitic diseases by means of chemical drugs, has made considerable progress during the last few years. Such diseases may be caused by the presence in our bodies of large parasites, *e.g.* tape-worms, liver flukes and hook-worms, or of parasites of microscopic dimensions. Among the latter are included (*a*) **protozoa,** animal micro-organisms with relatively large and highly developed cell structures, (*b*) **bacteria** and *fungi,* which are appreciably smaller than protozoa and are generally classed as vegetable micro-organisms, and (*c*) the exceedingly small **filter-passing viruses,** which are so minute as to pass through the pores of unglazed porcelain. The aim of the treatment is to discover a remedy which will kill the parasites without unduly endangering the life of the patient, and although notable successes have already been achieved in this field they have been limited until recently to diseases originating in the presence of large parasites and of protozoa.

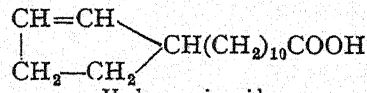
Protozoal Diseases.—Some outstanding examples of protozoal diseases, together with their remedies, are tabulated below.

Malaria	Quinine, plasmoquine, atebrin.
Syphilis	Salvarsan (neoarsphenamine), sulpharsphenamine.
Sleeping sickness . . .	Atoxyl, tryparsamide, germanin (see p. 852).
Yaws	Neoarsphenamine.
Kala-azar	Tartar emetic.
Amœbic dysentery . .	Emetine.

Bacterial Diseases.—In most of the above cases of protozoal disease the remedies are highly effective and their discovery represents an invaluable contribution to medicine. Until a few years ago, however, little corresponding progress had been made in the chemotherapeutic treatment of bacterial diseases, which are an even greater scourge to mankind than those of protozoal origin. Leprosy, a bacterial disease due to *B. lepræ,* was formerly treated by oral administration of the nauseating *chaulmoogra oil.* Real progress with this disease has only been made since 1910, when the method of injecting *sodium hydnocarpate*



Chaulmoogric acid

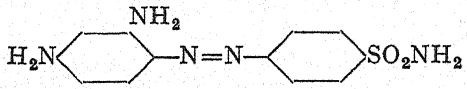


Hydnocarpic acid.

into the muscles was introduced, this salt being later replaced by the more effective **ethyl chaulmoograte.** In this way cures can now be effected in 40 to 50 per cent. of the cases.

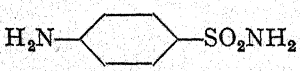
In 1935 Domagk, working with the Bayer Company at Elberfeld, Germany, aroused widespread interest in the medical world by making

known the astonishing results obtained with prontosil in curing certain streptococcal infections. While investigating the use of azo dyes in this connection, Domagk discovered that azo compounds containing sulphonamido groups had a marked beneficial effect. **Prontosil,** the hydrochloride of 4-sulphonamido-2′: 4′-diamino-azobenzene (see annexed formula) proved to be the most active of the very large number of sulphonamido dyes under examination.



In their various strains streptococcæ are responsible for the majority of septic conditions such as are present in blood-poisoning, wound infections, and many major diseases, including erysipelas, scarlet fever, puerperal fever, pneumonia, cerebrospinal meningitis, gonorrhœa, and tonsillitis. In most cases the infection is due to *Streptococcus pyogenes*, the β-hæmolytic streptococcus. Pneumonia is more generally caused by the *pneumococcus* or *Streptococcus pneumoniæ*. It will be readily understood that the discovery of drugs capable of being used with success in the treatment of any of these diseases represents an advance in chemotherapy of the greatest significance.

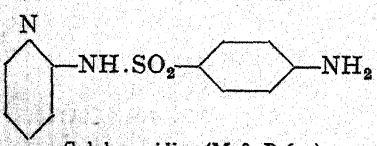
Later developments furnish an interesting example of the manner in which such problems are attacked by research chemists working in collaboration with pathologists. It was found in France that prontosil breaks down in the human body to form *p*-aminobenzene-sulphonamide, and that the latter compound was an equally active chemotherapeutic agent. The importance of this lies in the fact that p-*aminobenzene-sulphonamide*, now usually called **sulphanilamide,** has long been known to chemists and is not a patented product. It is, moreover, cheap and can therefore be used in place of the highly priced prontosil.



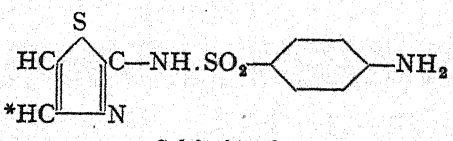
Sulphanilamide.

After it had been shown that benzene sulphonamide itself, with no amino group in the para position, was completely inactive, research was directed towards the investigation of derivatives of sulphanilamide in which hydrogen of the amino groups was replaced by substituents. Among numerous compounds of this type two of outstanding activity have been found, namely **sulphapyridine** (M & B 693), and **sulphathiazole,** both prepared in the laboratories of May and Baker.

A homologue of the latter, **sulphamethyl-thiazole** (M & B 760a) is also used, containing a methyl group in place of the hydrogen atom marked with an asterisk.



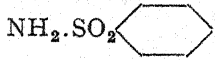
Sulphapyridine (M & B 693)



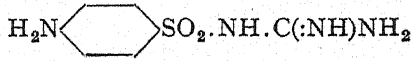
Sulphathiazole.

Medical evidence up to the present time indicates that in the treatment of most streptococcal diseases sulphanilamide, prontosil and sulphapyridine are equally and remarkably effective. As sulphanilamide is cheap it is generally employed in preference to the other two in all cases except that of pneumonia, for which sulphapyridine alone is of value. The sulphathiazoles are expensive to manufacture and do not appear to possess any great advantage, although they produce less nausea and are somewhat more active against staphylococci.

Two sulphanilamides which have been more recently introduced are **Sulphonamide EOS** (A. G. Green and M. Coplans) and **Sulphanilyl guanidine.** The former is prepared by heating sulphanilamide with a



Sulphonamide EOS



Sulphanilyl guanidine.

concentrated solution of sodium acetaldehyde bisulphite. It dissolves readily in water, is rapidly absorbed, and has less tendency to produce sickness than the above-mentioned derivatives. Good results have been recorded by its use in the treatment of cerebrospinal meningitis. Sulphanilyl guanidine has been employed with great success as an internal antiseptic in cases of dysentery.

Sulphanilamides are administered in comparatively large doses by mouth or by dusting on an infected wound, and the results are usually rapid and decisive. Astonishing reductions in mortality have been recorded by their use in puerperal fever, pneumonia and cases of severe blood poisoning. The mortality rate for cerebrospinal meningitis or spotted fever, which was about 60-70 per cent., has latterly been lowered to the order of 30 to 40 per cent. by use of serums. Sulphanilamide, however, has now brought this rate down to the neighbourhood of 2 per cent. Sulphapyridine, which is reducing the death rate in pneumonia cases to about one-third of the earlier figure, has also proved to be of special value as a remedy for gonorrhœa, a disease for which no satisfactory treatment had hitherto been evolved. Encouraging results have already been obtained with infections due to *B. coli* and with plague. Among other bacterial diseases which have not yet been successfully treated by chemotherapeutic methods are tuberculosis, whooping cough, typhoid, paratyphoid and cholera.

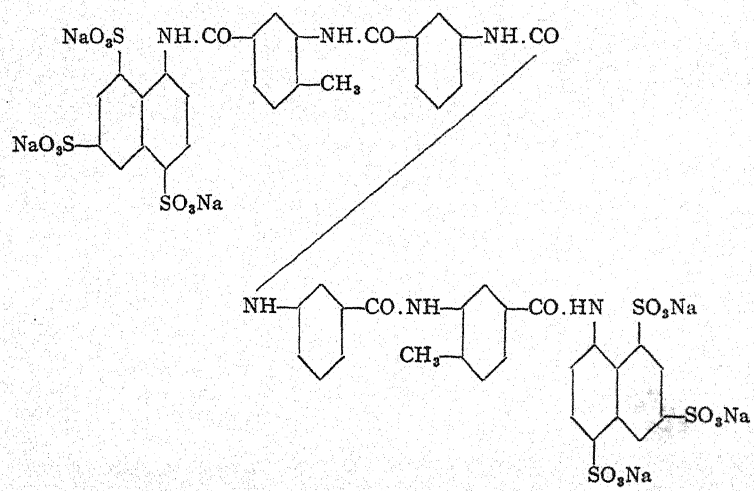
One of the great disadvantages of serums is that they are very specific in their reaction. Not only must different diseases, if they are amenable to this type of treatment, be countered by use of their particular serums, but a given disease may be caused by different strains of the same bacillus, in which case it is generally necessary for the latter to be identified before an appropriate serum can be selected. There are, for example, no less than 34 known strains of *pneumococcus* which may give rise to pneumonia. Fortunately it has been found that sulphapyridine is equally effective against all of these. Further research indicates that the strains differ

from one another only in the nature of the outer protective coverings which enclose the pneumococcus protoplasm. The outer layers are composed of material resembling the vegetable gums and can apparently be permeated by sulphapyridine by virtue of the pyridyl group which differentiates it from unsubstituted sulphanilamide.

Virus Diseases in general have not yet been attacked with any great success by chemotherapeutic methods. In this group are included small-pox, measles, infantile paralysis, colds and influenza, together with certain animal diseases such as foot-and-mouth disease and canine distemper.

The sulphanilamide drugs suffer from the disadvantage that they occasionally damage the bone marrow which is responsible for the production of the white cells of the blood. This condition is dangerous, but it may be guarded against by an examination of the blood and discontinuance of the treatment if necessary. It is an interesting point that the sulphonamides have no very strong antiseptic action outside the animal and that their remarkable activity is only exerted in the presence of blood serum.

Unfortunately, no working theory has yet been developed to explain why one particular arrangement of atoms should be more effective than another in attacking a given micro-organism. Why, for example, is the *p*-aminobenzene-sulphonamide group so amazingly active against streptococcal infections? Why is the efficiency of germanin (formulated below) in the treatment of sleeping sickness wholly dependent on two otherwise insignificant methyl substituents, in the absence of which the remaining molecular structure is practically inactive? Until some reply to questions such as these is forthcoming, chemotherapy can only advance slowly and along empirical lines.



Germanin, Bayer 205.

XIII

Synthetic Resins or Plastics[1]

The remarkable success of the phenolic aldehyde resins introduced by Baekeland has resulted in an enormous development in the group of compounds known as plastics or synthetic resins. Under this heading are included not only plastic materials and those which become plastic on heating, but also hard infusible products which at some stage in their preparation have plastic properties by means of which they can be moulded into finished articles. They are produced by the polymerisation or condensation of relatively simple compounds and represent a number of different chemical types. High polymers are unique among organic materials in possessing an exceptional degree of tensile strength, elasticity, hardness and toughness, as has long been recognised in the case of the natural polymers, silk, cotton, rubber and shellac. By the use of synthetic methods it is now possible to prepare on the large scale products with any of these valuable mechanical qualities.

Plastics vary greatly in their physical properties, ranging from black or bright in colour to glass-clear and from a viscous or rubbery consistency to hard or even brittle. All are capable of being employed for the manufacture of moulded articles, although some are better adapted for use as protective finishes in lacquers and dopes, or for bonding loose materials such as asbestos and mica in a form which will withstand high temperatures (*e.g.* for insulations, brake linings). Owing to their excellent electrical properties many members of the group are used as insulating materials ; others such as *perspex*, which are transparent and colourless, may be moulded directly into optical lenses or used as windows in aircraft. The solid forms may be not only moulded but also sawn, cut, turned and polished.

According to their nature it is usual to divide plastics into two main groups, namely the thermoplastic and the thermosetting resins.

Thermoplastic resins.—These are soluble in organic solvents and are fusible ; they may be shaped and reshaped repeatedly by the application of heat followed by treatment of the softened or liquid mass in a mould. In this class are included most of the earlier known natural resin and wax compositions, such as *shellac* (still used for gramophone records), *bitumen plastics* (screw stoppers of bottles, etc.) and *cellulose plastics* (celluloid, cellulose acetate and ethers) as well as the more recent glass-like *plastics prepared from the vinyl derivatives, styrene, acrylic and methacrylic esters, and methylene ketones.*

Thermosetting resins.—Products of this type have undergone polymerisation or condensation during treatment in the heated mould

[1] See *Trans. Farad. Soc.*, 1936, **32**, 1-412 ; *Plastics*, by V. E. Yarsley and E. G. Couzens, (Pelican Books, 1941) ; *The Development of Nylon*, E. K. Bolton, *Chem. and Ind.*, 1942, **61**, 31.

so as to form insoluble and infusible materials, which cannot be further reshaped by heat or pressure. In this group are the *bakelites or phenolic plastics, amino or urea plastics, and the glyptals or alkyd resins.*

Polymerisation and Condensation Processes

The monomeric starting material, as will be seen later, is not necessarily a homogeneous product but may be a mixture of two or more compounds. Polymerisation [1] is effected by heat or light and is often assisted by the addition of *accelerators* (acids, bases, benzoyl peroxide, diisobutylene ozonide). Use is also made of *retarders* (picric acid, sulphur, nitro and nitroso compounds) which increase the time required for complete polymerisation, and of *inhibitors* (hydroquinone, phenyl naphthylamines) which cause a preliminary period of inhibition during which no polymerisation occurs. The various monomers undergo polymerisation at widely differing rates, and the change may be completed in a few seconds or may require hours. In many cases it is desirable to effect partial polymerisation before submitting the product to final treatment in the mould or other process. For these reasons it is essential to have the reaction under efficient control.

Polymerisation or condensation progresses by a species of chain reaction, leading to the formation of linear macro-molecules. In the thermosetting types these long chains eventually become cross-linked in all directions by shorter chains to give a rigid lattice arrangement. Little is known as to the nature of the terminal groups or the reason for the cessation of growth, although in the case of polystyrene Irany has suggested that termination occurs by the mutual deactivation of two active chains, with the formation of a double bond in the molecule. The physical properties of the final polymer largely depend upon the *number of active functions* or groups in the monomeric molecules employed as the starting material. In this respect a distinction is drawn between bifunctional monomers, which yield thermoplastic resins and polyfunctional monomers, which form resins of the thermosetting type.

Bifunctional Monomers.—An example of this kind is the hydroxy acid HO.R.COOH, containing the two active groups hydroxyl and carboxyl. The acid, on being heated, undergoes condensation with loss of water to form a linear polyester [2] of the structure

$$HO.R.CO.O.R.CO.O.R.CO.O.R.CO \ldots\ldots\ldots O.R.COOH.$$

A similar chain reaction occurs when a glycol and a dibasic acid (both bifunctional) are heated together,

$$HO.CH_2.CH_2.OH + HOOC.R.COOH \longrightarrow$$
$$HO.CH_2.CH_2.O.CO.R.CO.O.CH_2.CH_2.O.CO.R.CO.O.CH_2 \ldots\ldots$$

[1] Carothers has pointed out that in modern usage the term polymer is now being employed to include condensation products which are not of the same empirical composition as the monomeric starting material (see, for example, paraformaldehydes).

[2] It is clear that the structures of the reactants may be such as to lead to the formation of closed rings, in which case the product is deactivated and no further growth takes place.

A detailed investigation of such types was made by Carothers and his co-workers, which led to the examination of polyamide chains containing hydrocarbon radicals linked by CO.NH-groups. Carothers found that the plastic properties of the polyamides are closely related to the lengths of the hydrocarbon radicals, and the work culminated in the development of the synthetic silk *Nylon* and the fibre *Exton*. *Nylon* can be obtained finer, stronger and more resistant than natural silk, which it resembles in molecular structure. As at present manufactured (see p. 859) it is a condensation product of hexamethylene diamine with adipic acid, and is of the general structure

$$\ldots\ldots NH.CO.R_1.CO.NH.R.NH.CO.R_1.CO.NH.R.NH.CO.R_1.CO.NH\ldots\ldots$$

Another important example of a bifunctional compound is styrene, $C_6H_5.CH:CH_2$, the polymerisation of which is believed to proceed by way of the activated form $—CH(C_6H_5).CH_2—$ to yield polystyrene chains of the type

$$\ldots\ldots —\underset{\displaystyle C_6H_5}{\underset{|}{CH}}—CH_2—\left[\underset{\displaystyle C_6H_5}{\underset{|}{CH}}—CH_2\right]_n—\underset{\displaystyle C_6H_5}{\underset{|}{CH}}—CH_2— \ldots\ldots$$

All the above cases refer to monomers having only two active functions, and the resulting polymers are mixtures of long chain molecules of various lengths. The structural pattern may thus be described as one-dimensional. Such polymers are in general both soluble in organic solvents and fusible; all products of this nature are **thermoplastic.**

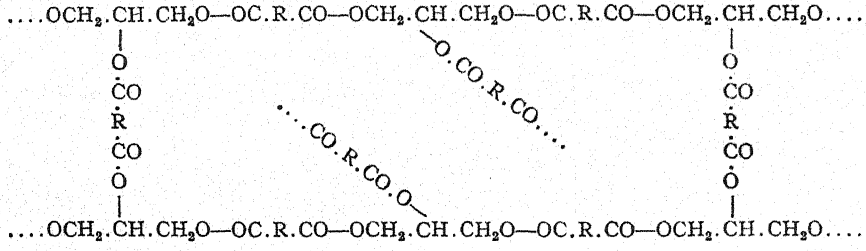
On examination, it is found that these synthetic resins differ from cellulose in giving no definite X-ray diffraction pattern, and it must be assumed that the long chain molecules are not oriented in parallel lines but have a tangled arrangement. Lack of a regular pattern may also be due in part to the formation of isomeric structures through branching of the chains. The van der Waals forces of attraction between macromolecules of this kind are very considerable, however, so that after being softened by heat the cooled viscous mass may be stretched out into long threads, in which owing to partial slipping of the chains past each other the molecules become to some extent oriented in parallel directions.[1] This orientation leads to an increase in lustre and tensile strength (see Nylon, p. 859).

When a resin of this type is treated with a solvent, the molecules of the latter are also attracted to those of the polymer by the van der Waals forces. As a result the solvent penetrates slowly into the mass, which at first swells and then as the chains become separated eventually passes into solution. Small amounts of a selected solvent are often added to a polymer for the purpose of softening the material or to render it less brittle. For this reason camphor is added to pyroxylin in the manufacture of celluloid. But such **plasticizers** are generally non-volatile liquids,

[1] J. R. Katz, *Trans. Farad. Soc.*, 1936, **32**, 77. Compare also stretched rubber, p. 498.

e.g. triphenyl and tricresyl phosphates, butyl phthalate and triacetin (glyceryl triacetate).

Polyfunctional Monomers.—When, however, *reacting molecules with higher functions than two* are involved, as in the combination of glycerol (trifunctional) with a dibasic acid, the product has entirely different properties. Instead of the simple linear polyester obtained with glycol, the glyceryl ester is a rigid three-dimensional structure in which the long main chains are interconnected by cross-links in all directions, as symbolised in the following diagram where the inclined chains may be supposed to bind parts of the molecule situated behind or in front of the main diagram. This kind of product is insoluble and infusible and



belongs to the group of **thermosetting resins.** It cannot be remoulded by the further application of heat and pressure, and solvents are no longer able to effect a separation of the chains, although a certain amount of swelling may occur in some cases. Complete elimination of swelling can be achieved by increasing the number of cross-links, but this also tends to make the product more brittle.

In some polymerisations and condensations the linear reaction predominates under mild experimental conditions, even when one of the reacting molecules has more than two active functions. This is useful technically as it allows the reaction to be carried out in two stages. Products varying by degrees from the readily soluble and fusible to the insoluble and infusible can thus be prepared according to the extent of interaction (see phenol-aldehyde condensations). Staudinger [1] has demonstrated the remarkable effect of polymerising styrene to which even so small a proportion as 0·01 per cent. of *p*-divinylbenzene, $CH_2:CH.C_6H_4.CH:CH_2$, has been added. The molecules of the latter, being polyfunctional, provide cross-links between the linear polystyrene chains, with the result that whilst the product outwardly resembles polystyrene it differs from it in being insoluble in solvents, although undergoing swelling in their presence. Pure divinylbenzene on polymerisation yields a hard brittle product, which does not swell in solvents and is readily powdered.

Thermoplastic Types

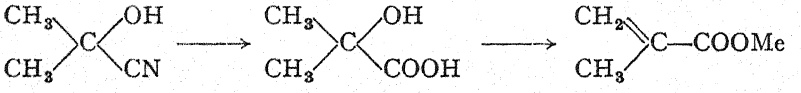
Celluloid, one of the earliest representatives of this group, has already been described (see Index).

[1] *Trans. Faraday Soc.*, 1936, **32**, 325.

Cellulose acetate is prepared for use by being mixed with the necessary amount of solvent and a plasticizer. It then forms a doughy mass from which excess of solvent is removed by working between hot rollers. Thick irregular sheets termed " hides " are thus obtained. For moulding purposes these are cut into fine chips and mixed with the required fillers and colouring matter. The thin sheets employed for wrappers are made by evaporating a dilute solution on a flat metal surface from which the film is subsequently stripped (*continuous film casting process*). The solvent is recovered for further use.

The newer *glass-like plastics* are vinyl derivatives which are most conveniently described under the individual monomeric starting materials.

Methyl methacrylate is employed in the production of *diakon* moulding powder and of *perspex*. For this purpose acetone cyanhydrin is converted into methacrylic ester by treatment with sulphuric acid at 100° to 110° followed by reaction with methyl alcohol.[1]



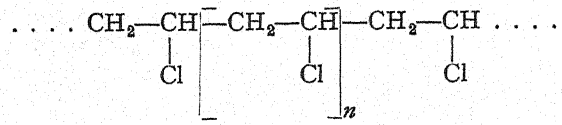
The resin, *diakon*, formed by polymerisation of the methyl methacrylate is powdered and used either for injection or compression moulding at a temperature of 130° to 190°, the moulding cycle being generally complete in about 1½ minutes. In the first of these processes the plastic is preheated and the semi-fluid material is then injected under high pressure into a cold mould ; in the second process the powdered product is compressed in an already heated mould. Whichever method is employed the moulded article cannot be removed before it has cooled sufficiently to become set. The polymer is also cast into rods and sheets ; in this form it is known as *perspex*.

The chief characteristics of *perspex* are its remarkable clarity, low specific gravity (1·19) and excellent mechanical and electrical properties. It is used for making electric fittings, telephones, dentures, etc., and protective windows for aircraft. Lenses of any desired prescription are readily moulded in a finished form ; they are rather more easily scratched than glass but may be surface-hardened by means of a clear uniform layer of silica deposited in a high vacuum, care being taken to screen the lens from direct heat. The polymer is also used for lacquers and dopes.

Vinyl chloride polymers are denser (sp. gr. 1·4) than perspex but are non-inflammable and more resistant. Owing to its higher melting point the product must be treated with a plasticizer before being used in moulding. Polyvinyl chloride is employed for the manufacture of chemical plant, pipe lines, water-resisting sheets and flexible insulations

[1] E. P. 405,699 (I.C.I., 1933). Cent., 1934, II, 3182.

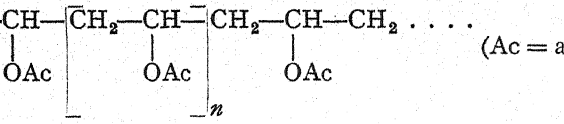
for wires and cables. The molecules are represented as containing chains of the type



Vinyl acetate can be prepared in 80 per cent. yield by the direct combination of acetylene and acetic acid in the presence of a mercury salt catalyst.

$$CH_3.COO.H + HC{\equiv}CH \longrightarrow CH_3.COO.CH{=}CH_2$$

It polymerises on heating to form a clear transparent mass, sp. gr. 1·2, and the process may be so controlled as to give products (*Gelvas*) of widely differing viscosities. The average molecular weight may range from about 5000 to 100,000. Polymerisation is represented as leading to chains of the following structure :

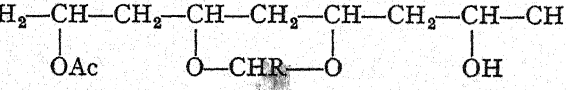


(Ac = acetyl group).

Polyvinyl acetate is somewhat low in melting point for use in moulding, but is employed for lacquers, finishing compositions and adhesives.

Vinyl acetate and vinyl chloride are also used in admixture for the preparation of polymers (*mixed or co-polymers*). By varying the proportions of the ingredients it is possible to obtain resins with a wide range of properties which are suitable for moulded articles.

A more recent development is to subject the pre-formed polyvinyl acetate to further chemical change.[1] Complete hydrolysis removes the acetate groups, leaving a polyvinyl alcohol (*Solvars*) ; by partial hydrolysis polymers of mixed functions are obtained with differing solubilities and viscosities. The hydroxylated compounds can be made to react with aldehydes (acetal formation) yielding *Formvars* from formaldehyde, *alvars* from acetaldehyde, *Butvars* from butyric aldehyde. These products may be generalised in the formula



To a minor extent the aldehyde molecules may also form cross-links between the polyvinyl chains. Such polymers are utilised as lacquers, adhesives and for moulding. *Formvars* and especially *Butvars* are employed as interlayers in laminated safety glass for automobiles.

Styrene, prepared from ethylene and benzene (see p. 382), is polymerised by means of heat, in some cases with the aid of an accelerator.

[1] See G. O. Morrison, *Chem. and Ind.*, 1941, pp. 209, 390.

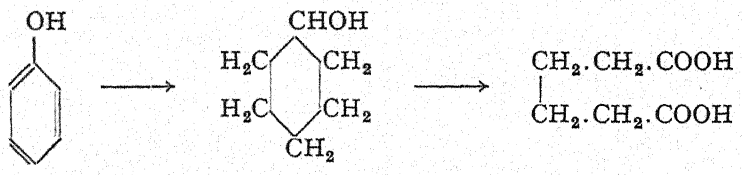
For the structure of the chain see p. 855. The polystyrene or *distrene* thus obtained has the very low specific gravity of 1·05; it softens about 70° to 90° and is used in fluid form at 160° to 180° for injection moulding. Being to all intents and purposes a saturated hydrocarbon, the polymer is strongly resistant to corrosion and oxidising agents. Its exceptionally good insulating qualities are not lost even after immersion in water. For these reasons the main use of styrene polymers is in the electrical industry.

Nylon, a synthetic fibre, was developed by Carothers and his co-workers in America as a result of preliminary investigations carried out on polyesters, such as those prepared by the condensation of glycol with a dibasic acid (see p. 854). It was found that the threads formed by dipping a rod into the molten polyester were brittle and of low tensile strength; but that when they were subsequently cold-drawn to several times their original lengths they became tough and could then be tied into knots without breaking. The drawing process also greatly increased the lustre and tensile strength. An X-ray examination showed that the cold-drawn fibres, unlike the original filaments, gave a definite diffraction pattern, proving that the treatment had brought about a considerable degree of orientation of the molecular chains parallel to the fibre axis. This discovery proved later to be of fundamental importance for the production of Nylon threads.

Nylon, also known as "66," was first synthesised in 1935. It is prepared by condensing hexamethylene diamine and adipic acid by heating them in an autoclave in the presence of stabilisers to control the molecular weight and viscosity of the final product. It is thus a polyhexamethylene-adipamide built up of recurring units of the structure

$$\ldots . \mathrm{NH.(CH_2)_6.NH.CO.(CH_2)_4.CO} \ldots .$$

The raw material for the preparation is phenol, which is reduced catalytically to cyclohexanol and the latter converted by oxidation into adipic acid.



Hexamethylene diamine is believed to be obtained from the adipic acid by a catalytic method.

The molten polymer from the autoclave is expressed in ribbon form, cooled and cut into chips. It is thus in a state suitable for storage and for the blending necessary to eliminate variations in individual batches. Nylon has a molecular weight of about 10,000 and melts at 263°. The latter figure is somewhat high for a thermoplastic resin, but resistance to heat is essential for a material which has to be submitted to washing and ironing. Spinning is carried out with the molten polymer at 285° in an

atmosphere of nitrogen (it can also be effected with a phenol solution) and the newly-formed threads are by a continuous process cold-drawn to about four times the original length. The resulting filaments have a high tensile strength, elasticity and lustre. They can be made finer, stronger and more resistant to chemical action than natural silk, or in larger diameters for use in the manufacture of bristles, for the replacement of gut in surgical sutures, racquet strings, fishing lines and for a variety of other purposes.

Thermosetting Types

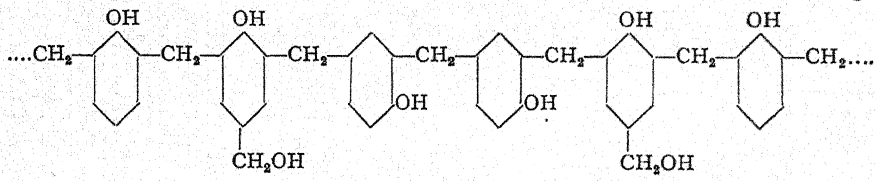
Although thermosetting resins cannot be remoulded, they have the advantage of being more resistant to solvent action and to high temperatures. They are made in two stages, and the final moulding process is a short heat treatment ranging from a few seconds to several minutes. With thermoplastic resins a longer period has generally to be allowed, in order that the mould may cool and its contents solidify.

Phenol-aldehyde plastics of the *bakelite type* are made by condensing a phenol with an aldehyde, usually phenol with formaldehyde. The first stage is carried out at about 70° in the presence of a catalyst such as ammonia or sulphuric acid and using a copper or stainless steel still. Water eliminated during the reaction is removed by distillation, and the fluid resin (*Novolak*) is run off and allowed to solidify. It is believed that the initial reactions are,

(1) $C_6H_5.OH + CH_2O \longrightarrow HO.C_6H_4.CH_2OH \xrightarrow{C_6H_5OH} HO.C_6H_4.CH_2.C_6H_4.OH + H_2O$. etc.

(2) $HO.C_6H_4.CH_2.C_6H_4.OH + CH_2O \longrightarrow HO.C_6H_4.CH_2.C_6H_3(OH)(CH_2OH)$

leading to a mixture composed of long chain molecules of irregular constitution and containing as yet uncondensed CH_2OH-groups,[1] *e.g.*



Novolaks prepared by a short heating process are fusible and soluble. These are used for the manufacture of cements, varnishes and laminated materials.

In the second stage the powdered *Novolak* is mixed with fillers such as wood flour, which give a greatly improved product, and with colouring matters; it is then moulded under compression at a high temperature. Phenol is a polyfunctional reactant, having one para and two ortho positions open to attack, and during the final moulding further condensation occurs in which new methylene groups derived from the uncondensed

[1] See N. J. L. Megson, *Trans. Farad. Soc.*, 1936, **32**, 336. The aldehyde may react in the hydrated form as $HO.CH_2.OH$.

CH_2OH-groups form cross-links between the molecular chains, giving a three-dimensional lattice.

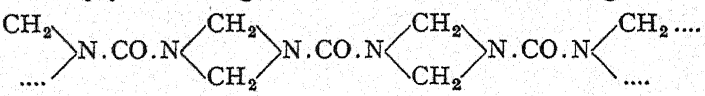
By the exercise of careful control the first stage of the preparation is broken off while the resin (Novolak) has still the necessary fluidity under heat and retains sufficient chemical reactivity to yield a well-shaped rigid product at a higher temperature in the mould.

Certain other phenols such as *m*-cresol, which has also one para and two ortho positions available, may be used as starting material, but *o*- and *p*-cresols are only bifunctional and are not by themselves capable of forming a thermosetting resin.

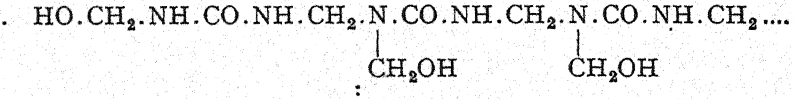
The applications of the phenol-aldehyde plastics for moulded articles are too many to be described in detail. It may be noted, however, that they are used very successfully for the manufacture of gear wheels, not only for small-scale work but also in cement plants, steel rolling and paper mills, where with water as lubricant they have proved more silent and much cheaper in the long run than gears made of metal. A disadvantage of the phenolic resins is their dark colour, hence white or brightly coloured articles are made from other types such as the urea-formaldehyde plastics.

Urea or amino plastics are prepared from urea and an aldehyde, often with the addition of thiourea. The first stage of the reaction is commonly carried out by dissolving urea in aqueous formaldehyde below 10° C., and then effecting condensation at about 130°. Water is subsequently removed under reduced pressure, and the molten resin is run off. The product is comparatively colourless, and after being mixed with fillers (wood flour or cellulose pulp) and brightly coloured dyes it is used for the final moulding process, during which cross-links are formed between the molecular chains and the material becomes infusible and insoluble (*Beetle ware*). The structure of the urea plastics is not definitely known, although the primary condensation products have been identified as *monomethylol-urea*, $NH_2.CO.NH.CH_2OH$, and *dimethylol-urea*, $HOCH_2.NH.CO.NH.CH_2OH$. It has been suggested that further condensation may yield arrangements [1] such as the following :—

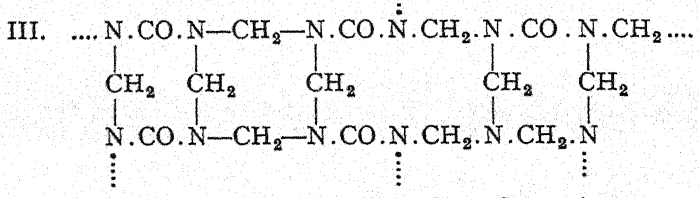
I.



II.



III.



[1] See G. Walter, *Trans. Farad. Soc.*, 1936, 377.

Glyptals or alkyd resins represent another type of synthetic resin obtained by the condensation of glycerol (glycol or mannitol) with an acid such as phthalic acid (isophthalic, tartaric, citric, succinic acid, etc.). The product forms a tough leathery mass at high temperatures which only becomes completely hard after prolonged heating and is therefore rarely used in a mould. Glyptals are employed in large quantities as bonding agents for asbestos, mica, etc., and other materials required to withstand high temperatures, such as brake linings and supports for heavy electrical windings. Unlike shellacs and the phenolic resins, which only form an external coating when applied to cotton and other fabrics, the glyptals penetrate into the pores of the material. Mixed plastics (*Paralacs*, *Bedesols*) of a different type are also made by combining glyptals with natural resins, *e.g.* copals, colophony, as well as with other synthetic resins and with drying oils. These are largely used for the manufacture of paints, lacquers and stoving enamels.

Statistics.—In 1938 it has been estimated that the approximate American output in metric tons was as follows: thermosetting resins, 20,000; synthetic resins of coal tar origin, 53,000 tons, and of non-coal tar origin, 12,000 tons. These quantities have already far outstripped the corresponding figures for celluloid (world output 30,000 tons in 1939) and for cellulose acetate (9,500 tons in 1937). Comparative figures for Great Britain and other countries are difficult to obtain, but the following data for synthetic resins have been given for 1937: Great Britain, 27,500 tons; Germany, 65,000 tons; U.S.A. 95,000 tons. An interesting point is that the production of alkyd resins in 1938 was already greater than that of the phenolic resins. Nylon has only recently come into production; the output in 1941 was 8,000,000 lb. and is increasing rapidly.

XIV

Deuterium Compounds

The isolation of the heavy hydrogen isotope, deuterium, by Urey in 1932 opened up an enormous field of investigation dealing with compounds in which hydrogen is displaced wholly or in part by deuterium. Many compounds of this kind have now been prepared and examined. In some of their physical properties such as melting point, boiling point, and optical activity these new derivatives differ very little from their ordinary prototypes; but in other properties such as density, solubility, dissociation constant and rate of reaction considerable variations may exist. At present it is doubtful if the substitution of deuterium for hydrogen is capable of giving rise to a sufficient degree of dissymmetry in an otherwise symmetrical compound for it to exhibit appreciable optical rotation. No such active compound has as yet been isolated.

Methods of Preparation.—Exchange reactions between hydrogen and deuterium represent one method of obtaining deutero-compounds and their study has already proved of value in the investigation of organic processes. Hydrogen in hydroxyl or amino groups is replaced extremely rapidly in the presence of deuterium oxide, *e.g.* $C_2H_5.OH \rightarrow C_2H_5.OD$; $CH_3.COOH \rightarrow CH_3.COOD$. Similarly the labile hydrogen in enolisable compounds is also exchanged, although more slowly, thus $CH_3.CO.CH_3 \rightarrow CD_3.CO.CD_3$; $CH_3.NO_2 \rightarrow CD_3.NO_2$. As is described in more detail later, the *deuteration* of hydrocarbons and hydrocarbon radicals, especially those of aromatic type, can be effected by use of more vigorous reagents such as deuterium sulphate or deuterium chloride, or in certain cases by means of deuterium in the presence of a catalyst like nickel or platinum. Unsaturated compounds have been converted into deutero-compounds by direct addition of deuterium under the influence of platinum catalyst, and methods have also been devised in which deuterium is introduced by synthetic reactions.

Tetradeutero-methane, CD_4, was prepared by Urey and Price [1] by interaction of aluminium carbide and D_2O. The reaction did not occur at room temperature, and even on heating it proceeded much more slowly than with water.

Dideutero-acetylene, C_2D_2, is formed from calcium carbide and deuterium oxide.[2] Here also the reaction occurred more slowly than with water.

Trideutero-acetic deuteracid, $CD_3.COOD$, was isolated by Wilson [3] using the following method :—

$$\underset{\text{Carbon suboxide.}}{C_3O_2} + D_2O \longrightarrow \underset{\substack{\text{Dideuteromalonic}\\ \text{deuteracid.}}}{CD_2(COOD)_2} \longrightarrow CD_3.COOD + CO_2$$

The intermediate **dideuteromalonic deuteracid** melted at 128° to 130° (decomp.) as compared with malonic acid, m.p. 134° to 135° (decomp.). Trideutero-acetic deuteracid obtained by heating the former compound melted at 15·75° and proved to be more volatile than acetic acid (m.p. 16·6°).

An attempt to prepare $CD_3.COOH$ by treating barium trideutero-acetate, $(CD_3.COO)_2Ba$, with sulphuric acid led to an exchange reaction which resulted in acetic acid as the main product (*Erlenmeyer*).

Acetic deuteracid, $CH_3.COOD$, is formed by interaction of silver acetate and deuterium chloride. It melts at 13·3° and has a much lower dissociation constant than acetic acid.

A number of other aliphatic deuterium compounds have been prepared, including alcohols, amines and nitro-compounds. **Trideutero-nitro-methane,** $CD_3.NO_2$, for example, is obtained when nitromethane is treated with D_2O. It has been found to enolise into the *aci*-form,

[1] *J. Chem. Phys.*, 1934, **2**, 300. [2] J. W. Murray, C. F. Squire and D. H. Andrews, *ibid.*, 1934, **2**, 714; F. W. Breuer, *J. A. C. S.*, 1936, **58**, 1289. [3] C. L. Wilson, *J. C. S.*, 1935, 492.

$CD_2:N(OD)O$, much more slowly than nitromethane.[1] Similarly **hexadeutero-acetone**, $CD_3.CO.CD_3$, undergoes enolic change at a slower rate than acetone. The latter compound has been shown to react with bromine at seven or eight times the speed of the deutero-compound, since bromination is here dependent on preliminary conversion into the enolic form. In the presence of comparatively concentrated D_2SO_4 (77 mols. per cent. in D_2O) aliphatic hydrocarbons may undergo partial deuteration.[2] The rate and extent of the change depend greatly on the structure of the hydrocarbon. Thus methylcyclohexane, containing a tertiary hydrogen atom is more readily deuterated than cyclohexane itself. Comparative reactivities are expressed in the sequence: methylcyclohexane > *n*-hexane > *n*-heptane > cyclohexane.

Hexadeuterobenzene, C_6D_6, was first obtained by the polymerisation of dideuteracetylene, $3C_2D_2 \rightarrow C_6D_6$, a process which Clemo has shown to be catalysed by tellurium oxide.[3] It may also be prepared by interaction of benzene and deuterium chloride in the presence of aluminium chloride[4]; by the exchange at higher temperatures between benzene and deuterium oxide using nickel as catalyst[5]; and by heating the calcium salt of mellitic acid with calcium deuteroxide,[6] $C_6(COO)_6Ca_3 + 3Ca(OD)_2 \rightarrow C_6D_6 + 6CaCO_3$.

In its purest form hexadeuterobenzene has been prepared by the exchange method of Ingold, Raisin and Wilson,[7] by shaking benzene at ordinary temperatures with D_2SO_4 (from SO_3 and D_2O) in a concentration of 51 mols. per cent. in deuterium oxide: $C_6H_6 + D_2SO_4 \rightleftharpoons C_6H_5D + DHSO_4$, etc. Four successive treatments over a period of 3 to 4 days gave a hexadeuterobenzene containing only about 1 per cent. of pentadeuterobenzene.

Hexadeuterobenzene . .	m.p. 6·8°; b.p. 79·3°; d_4^{25} 0·9429
Benzene	m.p. 5·5°; b.p. 80·1°; d_4^{25} 0·8735

Pentadeuterobenzoic acid, $C_6D_5.COOH$, has been produced from hexadeuterobenzene by bromination followed by an application of the Grignard reaction[8]: $C_6D_6 \rightarrow C_6D_5Br \rightarrow C_6D_5MgBr \rightarrow C_6D_5COOH$. It melts at 120·9° and is more soluble in water than benzoic acid (m.p. 121·7°). The dissociation constant of $C_6D_5.COOH$ differs little from that of benzoic acid, in striking contrast to the case of acetic deuteracid, $CH_3.COOD$, where the introduction of deuterium into the carboxyl group greatly diminishes the acid strength.

Benzoic acid readily exchanges the carboxylic hydrogen atom for deuterium in contact with heavy water, forming **benzoic deuteracid**,

[1] O. Reitz, *Z. physikal. Chem.*, 1936, A 176, 363. [2] C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. C. S.*, 1936, 1637. [3] Murray, Squire and Andrews, *loc. cit.*; G. R. Clemo and A. McQuillen, *J. C. S.*, 1935, 851. [4] A. Klit and A. Langseth, *Z. physikal. Chem.*, 1936, 176, 65. [5] P. I. Bowman, W. S. Benedict and H. S. Taylor, *J. A. C. S.*, 1935, 57, 960. [6] H. Erlenmeyer and H. Lobeck, *Helv. Chim. Acta*, 1935, 18, 1464; 1936, 19, 336. [7] *J. C. S.*, 1936, 915. [8] H. Erlenmeyer, H. Lobeck and Epprecht, *Helv. Chim. Acta*, 1936, 793.

$C_6H_5.COOD$. Benzyl alcohol [1] similarly yields the compound $C_6H_5.CH_2OD$.

Octadeutero-naphthalene, $C_{10}D_8$, has been isolated by Clemo and Robson [2] from the polymerisation products of dideuteracetylene. It melts at 80° to 81° as compared with naphthalene, m.p. 80°, and like the latter forms a picrate.

Orientation of Deuterium in Derivatives of Benzene

Ingold and co-workers have shown that the deuteration of a benzene derivative resembles the majority of aromatic substitutions in being an electrophilic process.[3] Deuterium seeks a point in the nucleus at which there is a high electron-availability (*cf.* p. 369) and the rate of deuteration increases with the power of the reagent to donate deuterons, *e.g.* $D_2SO_4 > D_3\overset{+}{O} > CH_3.COOD > D_2O$. The influence exerted by a substituent group on the rate and point of attack is found to be the same as that holding for other substitutions; for example, the relative effect of groups in facilitating or retarding deuteration is given by $\overset{-}{O} > NMe_2 > OMe > H > SO_3H$.

Phenol in the presence of heavy water rapidly exchanges one hydrogen for deuterium (OH→OD), and on addition of alkali three more may be replaced.[4] Subsequently it was proved that the last three deuterons enter the *o*- and *p*-positions, since on brominating the resulting deutero-compound a 2 : 4 : 6-tribromophenol is obtained containing no deuterium; deuterated aniline, $C_6H_2D_3.NH_2$, behaves in a similar manner.[5]

Münzberg [6] has examined the reaction between deuterium oxide and various polyhydroxybenzenes. With resorcinol the two hydroxylic hydrogens are rapidly displaced by deuterium, followed by the slow entry (greatly accelerated in N/10 alkali) of two deuterium atoms into the nucleus. Considering that there are three available *o*- and *p*-positions, it is curious that only two nuclear points appear to be readily attacked. Other compounds of this type behave more in accordance with expectation. In quinol four nuclear hydrogens are exchanged, in pyrogallol two and in phloroglucinol three.

Optical Activity and Deuterium Compounds.[7]—Information under this head may be subdivided into three main groups, dealing with (*a*) compounds whose asymmetry is due to the replacement of hydrogen by deuterium, (*b*) the effect of displacing hydrogen in an active compound by deuterium, and (*c*) the influence of solvents containing deuterium.

(*a*) In this group many attempts have been made to prepare optically active compounds, the asymmetry of which is solely due to the difference between hydrogen and deuterium. Only a few of these can be mentioned

[1] M. Harada and T. Titani, *Bull. Soc. Chem., Japan*, 1936, 11, 465. [2] *J. C. S.*, 1939, 429. [3] Ingold, Raisin and Wilson, *J. C. S.*, 1936, 1637. [4] P. A. Small and J. H. Wolfenden, *J. C. S.*, 1936, 1811. [5] A. P. Best and C. L. Wilson, *J. C. S.*, 1938, 28. [6] F. K. Münzberg, *Z. physikal. Chemie*, 1936, **B** 33, 23, 39. [7] For a survey see C. Buchanan, *Chem. and Ind.*, 1938, 748.

here. *d*-2-Brom-1-methyl-1-phenylethane, $C_6H_5.CH(CH_3).CH_2Br$, was converted by Grignard reaction into $C_6H_5.CH(CH_3).CH_2D$, but the product was inactive (Burwell, Hummell and Wallis). The halogen in *l*-bornyl chloride has been replaced by deuterium (CHCl→CHD) to form 2-deutero-camphane, again with loss of all optical activity (Biilmann). Attempts to resolve α-pentadeuterophenyl-benzylamine, $C_6H_5.CH(C_6D_5).NH_2$, led at first to a very small activity which was subsequently discounted; in the light of later work the authors state that the results are inconclusive (Clemo and co-workers [1]). The active carbinol, $CH_3.CH_2.CHOH.C:CH$, on treatment with deuterium in the presence of PtO_2 was converted into $CH_3.CH_2.CHOH.CD_2.CHD_2$, which was devoid of activity (McGrew and Adams). Another method of attack involves the use of one asymmetric centre to induce another. *l*-Phenyl-vinyl-carbinol, $CH_2:CH.CHOH.C_6H_5$, was reduced with deuterium to give a saturated alcohol, $CH_2D.CHD.CHOH.C_6H_5$, in which a new centre of asymmetry (at CHD) has been created under the influence of the active grouping already present. On fractionating the 3 : 5-dinitrobenzoic ester of this alcohol, hydrolysing the least soluble fraction and oxidising the : CHOH group to : CO in order to remove the original centre of asymmetry, the resulting ketone proved to be optically inactive.[2] A number of other negative results have been recorded and it must therefore be concluded that the optical rotation of compounds of this type is exceedingly small. That it is not entirely non-existent appears to be indicated by the result of molecular changes such as those described in the following paragraph.

(*b*) When hydrogen in an optically active compound is replaced in part by deuterium a small but measurable change in optical rotation usually results. A typical case is that of the active NN-dideutero-α-methyl-benzylamines, $C_6H_5.CH(CH_3).ND_2$, investigated by Young and Porter, in which the introduction of the two deuterium atoms reduced the rotation $[\alpha]^{20}_{5461}$ from +44·66° to +42·88°. In another example,[3] methyl-*n*-hexyl-carbinol of rotatory power +11·80° gave the deutero-compound $CH_3.CH(C_6H_{13}).OD$ with the value +11·62°.

(*c*) Comparative rotatory powers have been determined for a number of compounds in water and in deuterium oxide. Thus methyl-isopropyl-phenyl-benzyl-ammonium nitrate [4] in water has $[\alpha]^{20}_D$+114·1°, and in D_2O (91 per cent.) the value is +113·3°. Methyl *d*-mandelate [5] in C_6H_6 has $[\alpha]^{20}_D$+252·88°, which is reduced to+251·32° in C_6D_6.

Investigation of Reaction Mechanism by use of the Oxygen Isotope

Heavy oxygen has been employed as an " indicator atom " to determine

[1] G. R. Clemo and A. McQuillen, *J. C. S.*, 1936, 808; Clemo, R. Raper and A. C. Robson, *J. C. S.*, 1939, 431. See also R. Adams and D. S. Tarbell, *J. A. C. S.*, 1938, 60, 1260. [2] J. B. M. Coppock, J. Kenyon and S. M. Partridge, *J.*, 1938, 1069. [3] Young and Porter, *J. A. C. S.*, 1937, 59, 328, 1437. [4] H. Erlenmeyer and Schenkel, *Helv. Chim. Acta*, 1936, 1381. [5] *Ibid.*, 1938, 914.

the course of hydrolysis and of esterification. The alkaline hydrolysis of an ester might be supposed to proceed in either of the following ways :—

(1) $CH_3.CO:OR + H:O^{18}H \longrightarrow CH_3.COO^{18}H + R.OH$

(2) $CH_3.COO:R + HO^{18}:H \longrightarrow CH_3.COOH + R.O^{18}H$

By making use of water containing the heavy oxygen isotope Polanyi and Szabo [1] found that the alkaline hydrolysis of amyl acetate takes place by the first process, since the amyl alcohol liberated contains the normal oxygen isotope O^{16}.

Roberts and Urey [2] examined the esterification of benzoic acid with methyl alcohol, $CH_3O^{18}H$, in the presence of hydrogen chloride. The reaction takes the course,

$$C_6H_5.CO:OH + H:O^{18}CH_3 \longrightarrow C_6H_5.COO^{18}CH_3 + HOH.$$

Heavy oxygen has also been used to gain information regarding other possible reactivities of keto-compounds. For example, Herbert and Lauder find that acetaldehyde combines rapidly with water to give an equilibrium mixture :

$$CH_3.CH:O + H_2O \rightleftharpoons CH_3.CH(OH)_2$$

although no similar reaction in the sense,

$$CH_3.COOH + H_2O \rightleftharpoons CH_3.C(OH)_3$$

occurs with acetic acid under ordinary conditions.[3] On the other hand, Roberts concludes that a slow interchange with acetic acid takes place in the presence of hydrogen chloride.[4]

[1] *Trans. Farad. Soc.*, 1934, 30, 508. [2] I. Roberts and H. C. Urey, *J. A. C. S.*, 1938, 2391. [3] J. B. M. Herbert and I. Lauder, *Trans. Farad. Soc.*, 1938, 34, 432, 1219. [4] *J. Phys. Chem.*, 1938, 6, 679.

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